DISEASES of the CHEST

VOLUME 40 SEPTEMBER, 1961 NUMBER 3

Serum Protein Abnormalities in Neoplastic and Non-Neoplastic Disease of the Lung*,**

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Introduction

Significant abnormalities of the serum proteins are associated with a wide variety of chest diseases. In our experience they have been useful aids in the differential diagnosis of common as well as more obscure chest diseases, but more particularly, in prognostication and as an objective measure of disease activity and response to therapy.

This report will be concerned with the application of serum protein analysis to clinical chest disease and the probable clinical significance of some typical patterns which have been observed.

Materials and Methods

The serum protein profile (SPP) (Fig. 1) illustrates the results of a battery of protein determinations which are represented in a graphic manner for simple interpretation of the degree of normality or abnormality of a given protein value.

The profile includes a quantitative C-reactive protein determination made by means of gel-diffusion,[1] a serum antiprotease level using the antichymotrypsin method of West,[2] total serum protein,[3] total serum glycoprotein,[3] seromucoid,[3] seromucoid hexose,[3] and paper electrophoretic analysis of protein and glycoprotein with the Spinco system, using bromphenol blue (BPB), periodic acid-Schiff (PAS) stains, and the Model RB Analytrol for quantitation.[4]

The resultant test values are plotted on standardized scales which have been constructed so that a central solid line intersects each scale at the normal mean value, while the dotted lines intersect at one, two, and three standard deviations above and below the mean. For scales having two vertical lines, the figures on the left represent relative per cents for each fraction, and the figures on the right represent grams per cent protein and milligrams per cent glycoprotein.

For clinical usage the relative per cent values are plotted in blue pencil and the absolute values are plotted in red pencil. In the illustrations,

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The study was supported by Contract No. SA-43-ph-2436 from the National Cancer Institute and by a grant from the California Institute for Cancer Research.
**Presented at the 26th Annual Meeting, American College of Chest Physicians, Miami Beach, June 8-12, 1960.

only the grams and milligrams per cent values are plotted. By a glance at the graph, the clinician can immediately determine the presence of a significant protein abnormality. By comparing a given "suspicious" value to the "per cent" scale to the left of the other scales, the degree of abnormality can be determined. This scale gives the per cent of a normal population having values below a given value at the same level on the other scales. The scales are grouped so that the upper graph represents the non-electrophoretic determinations and the middle and lower graphs represent the values of the proteins and glycoproteins, respectively, as determined by paper electrophoresis. Because of limitations of space, values for most of the patients reported here are given in tabular form (Table 1).

The immunoelectrophoretic patterns were obtained by the micro-technique of Scheidegger[5] using Hyland (anti-normal whole human serum) antiserum.

TABLE 1—NUMERICAL VALUES FOR THE SERUM PROTEIN PROFILES

Patient No.	Protein Diagnosis	C-Reactive Protein	Serum Chymotrypsin Inhibitor (min.)	Total Serum Protein gm. per cent	Total Serum Glycoprotein mg. per cent Hexose	Seromucoid mg. per cent Hexose	Seromucoid Hexose mg. per cent	Glycoprotein: Total Serum Protein Ratio	Seromucoid Hexose: Seromucoid Ratio
1	Minimal pulmonary tuberculosis	neg.	6-0	7.4	128	105	22	17.3	.20
2	Chronic pulmonary emphysema	0.13	7-¾	6.6	117	70	12	17.8	.17
3	Chronic bronchitis	0.19	3-½	7.8	137	100	16	17.6	.16
4	Chronic bronchitis	0.22	8-¼	6.9	138	—	18	20.0	—
5	Minimal pulmonary tuberculosis	0.21	7-¾	6.5	140	—	—	21.6	—
6	Moderately advanced pulm. tuberc.	0.22	6-0	8.5	157	—	21	18.5	—
7	Far advanced pulm. tuberculosis	0.19	7-½	8.8	156	—	—	17.7	—
8	Far advanced pulm. tuberculosis	neg.	6-½	7.1	111	84	20	15.6	.24
9	Pulmonary cyst	0.09	7-½	8.1	136	—	—	16.8	—
10	Disseminated coccidioidomycosis	0.22	4-¼	6.9	169	—	34	24.5	—
11	Atypical asthma	0.09	-	7.1	100	74	13	14.1	.18
12	Allergic asthma	neg.	3-½	7.6	129	103	18	16.9	.18
13	Allergic asthma	neg.	4-¼	7.9	115	76	14	19.0	.18
14	Bronchogenic carcinoma	0.23	18-¼	7.7	180	151	23	22.4	.15
15	Bronchogenic carcinoma	neg.	4-¾	6.7	147	88	21	22.0	.24
16	Hodgkin's Disease	0.40	30+	7.1	190	223	56	23.4	.25
17	Lymphoma	0.23	7-¼	8.3	156	128	23	18.8	.18
18	Carcinoma of the esophagus	0.28	8-0	7.0	187	152	23	26.7	.15
19	Lymphosarcoma	neg.	10-0	7.9	123	121	27	15.6	.22
20	Chronic lymphatic leukemia	0.21	5-¼	6.6	148	162	35	22.5	.22
21	Reticulum cell sarcoma	0.33	12-0	5.9	146	155	9	24.8	.06
	Normal mean	neg.	5.75	7.6	113	82	12.2	15.0	.16
	Standard deviation		1.25	.48	10.6	16	2.2	2.1	.02

TABLE 1 (Continued)

Protein Fraction in Grams per cent

	Albumin	Alpha-1	Alpha-2	Beta-1	Beta-2	Gamma-1	Gamma-2	Total Beta	Total Gamma
1	3.96	0.35	0.53	0.35	0.61	0.88	0.70	0.96	1.58
2	4.12	0.18	0.45	0.28	0.45	0.64	0.45	0.73	1.09
3	4.25	0.30	0.69	0.30	0.49	1.08	0.69	0.79	1.77
4	4.01	0.37	0.56	0.19	0.47	0.65	0.65	0.66	1.30
5	3.12	0.27	0.68	0.41	0.54	0.95	0.54	0.95	1.49
6	3.51	0.36	0.73	0.66	0.73	1.28	1.21	1.39	2.49
7	3.25	0.32	0.62	0.47	0.86	1.96	1.32	1.33	3.28
8	3.44	0.39	0.62	0.45	0.56	0.95	0.67	1.01	1.62
9	3.47	0.29	0.68	0.40	0.48	1.50	1.29	0.88	2.79
10	2.48	0.28	0.83	0.41	0.69	1.38	0.83	1.10	2.21
11	4.15	0.49	0.74	0.24	0.49	0.61	0.37	0.73	0.98
12	3.98	0.39	0.77	0.39	0.52	0.91	0.65	0.91	1.56
13	4.45	0.33	0.55	0.55	0.67	0.79	0.55	1.22	1.34
14	4.32	0.25	0.62	0.37	0.49	1.00	0.62	0.86	1.62
15	3.00	0.42	0.98	0.35	0.49	0.84	0.63	0.84	1.47
16	3.55	0.48	0.78	0.36	0.30	0.84	0.78	0.66	1.62
17	3.30	0.55	0.82	0.55	0.62	1.58	0.90	1.17	2.48
18	3.85	0.35	0.62	0.26	0.62	0.62	0.70	0.88	1.32
19	5.48	0.17	0.36	0.41	0.36	0.65	0.47	0.77	1.12
20	3.70	0.40	0.75	0.30	0.50	0.55	0.40	0.80	0.95
21	2.86	0.54	0.98	0.36	0.36	0.45	0.36	0.72	0.81
Normal mean	4.2	.32	.59	.41	.54	.85	.63	1.03	1.47
Standard deviation	.47	.06	.10	.10	.08	.16	.12	.14	.24

Glycoprotein Fractions in Milligrams Per Cent

	Albumin	Alpha-1	Alpha-2	Beta-1	Beta-2	Gamma-1	Gamma-2	Total Beta	Total Gamma
1	10	26	36	18	18	12	8	36	20
2	8	25	33	16	16	11	8	32	19
3	8	33	35	14	19	14	14	33	28
4	8	25	58	11	17	8	11	28	19
5	7	30	55	13	15	9	11	28	20
6	12	31	49	16	23	14	12	39	26
7	8	28	51	19	20	14	16	39	30
8	11	23	29	15	13	10	10	28	20
9	3	23	39	16	16	23	16	32	39
10	9	37	60	18	23	14	5	41	19
11	5	23	26	18	14	10	4	32	14
12	5	17	42	19	22	10	14	41	24
13	7	13	32	18	22	10	13	40	23
14	11	43	58	22	25	14	7	47	21
15	6	24	51	18	18	15	15	36	30
16	13	61	61	13	15	8	19	28	27
17	9	29	45	18	27	16	12	45	28
18	11	51	55	22	18	15	15	40	30
19	7	27	24	20	20	10	15	40	25
20	10	46	52	16	12	8	4	28	12
21	19	29	49	15	15	7	12	30	19
Normal mean	11.2	18.3	30.8	14.5	14.3	8.6	13.4	29.9	22.1
Standard deviation	3.1	3.2	5.6	2.4	3.0	2.5	2.5	4.8	3.6

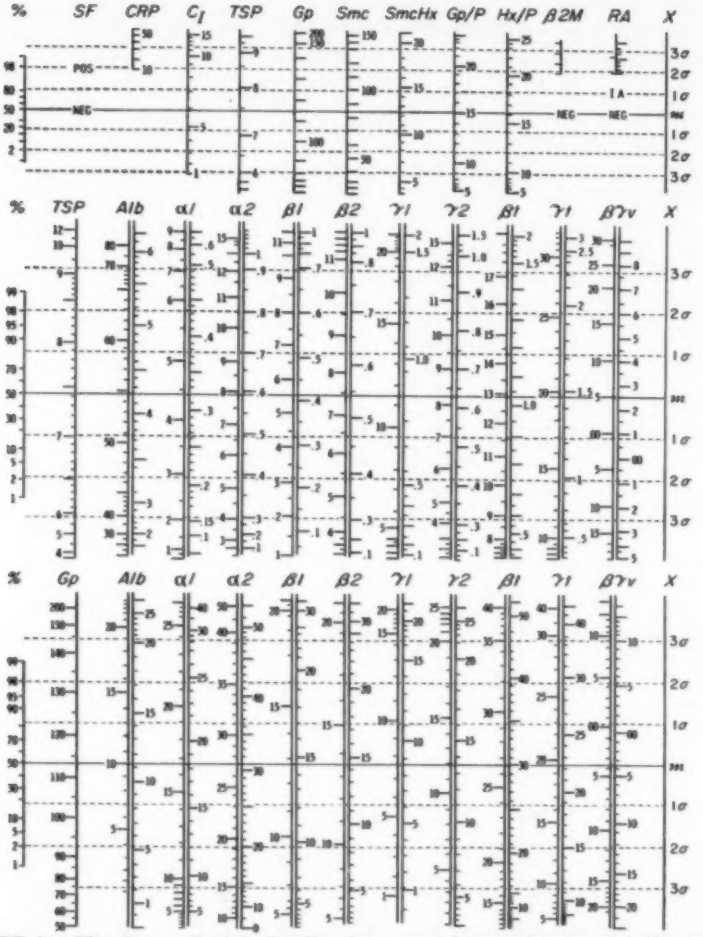

FIGURE 1: The Serum Protein Profile chart used for graphic presentation of the values of the various serum protein determinations. The left scale of each of the three sections gives the percentile of normal into which a given protein value at the same level on the other scale falls. The proteins represented by each scale are indicated by the abbreviation at the top of each scale.

Upper Section: CRP: C-reactive protein value determined by quantitative gel diffusion;[1] C_1: anti-chymotrypsin level in minutes;[2] TSP: total serum proteins;[3] Gp: total serum glycoprotein;[3] Smc: seromucoid;[3] SmcHx: seromucoid hexose:[3] Gp/p: glycoprotein/protein ratio; Hx/p: seromucoid hexose/seromucoid ratio; β2M: beta-2 macroglobulin level determined by gel diffusion (not used in this study); RA: titer of "rheumatoid factor" determined by the F II latex fixation test (not used in this study).

Middle Section: The left side of the double scales represents the per cent of total of each electrophoretic fraction. The right side of the double scales represents the amount of protein in each fraction in grams per cent. The scales include: Alb: albumin, α_1: alpha-one protein: α_2: alpha-2 protein; β_1: the beta-1 protein subtended by the anodal portion of the beta-protein peak; β_2: the beta-2 protein subtended by the cathodal portion of the beta peak; γ_1: the gamma protein subtended by the anodal protein of the gamma peak; γ_2: the gamma protein subtended by the cathodal portion of the gamma peak; β_t: the protein subtended by the beta peak; γ_t: the protein subtended by the gamma peak; $\beta_\gamma v$: a measure of the relative skewness of the beta and gamma peaks (not used in this study).

Lower Section: The scales represent the various electrophoretic fractions of glycoprotein and are analogous to the protein scales of the middle section.

The horizontal solid line intersects the scales at the mean value, and the horizontal broken lines intersect the scales at one, two, and three standard deviations above and below the mean.

Results

Glycoproteins were far more sensitive as an indicator of dysproteinemia than the protein pattern obtained with BPB stain. This is illustrated by a typical SPP of a patient with minimal pulmonary tuberculosis (Patient 1, Figure 2), whose protein pattern is normal, but who has a significantly elevated alpha-1 glycoprotein. In our experience the alpha-1 glycoprotein elevation is the initial and most transient indicator of subclinical inflammation.

A typical pattern (Patient 2, Fig. 3) obtained on serum from a patient with chronic pulmonary emphysema demonstrated this point. Although no clinically apparent infectious complication was evident, the significant elevation of alpha-1 glycoprotein probably represents the frequently

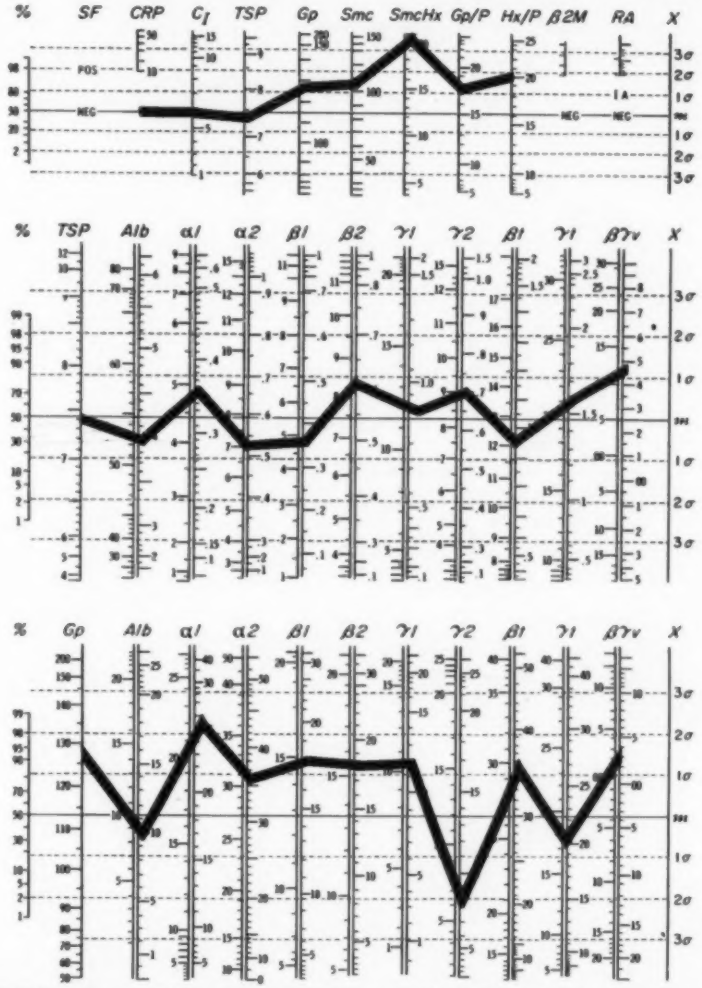

FIGURE 2: Serum protein profile (SPP) on a patient (No. 1, Table 1) with minimal pulmonary tuberculosis.

associated subclinical bronchitis. A pattern of a patient with chronic bronchitis of many years duration (Patient 3) also exhibited alpha-1 glycoprotein elevation. The serum from both of the latter patients, it should be noted, had relatively normal protein patterns.

In addition to the initial and transient alpha-1 glycoprotein elevation, when the inflammation persisted, and was severe enough to be clinically symptomatic, an elevation of the alpha-2 glycoprotein was usually observed. Another SPP (Patient 4) from a patient with chronic bronchitis demonstrated the simultaneous elevation of both alpha-glycoproteins, again associated with a relatively normal protein pattern. A similar glycoprotein pattern (Patient 5, Fig. 4) was seen in minimal pulmonary

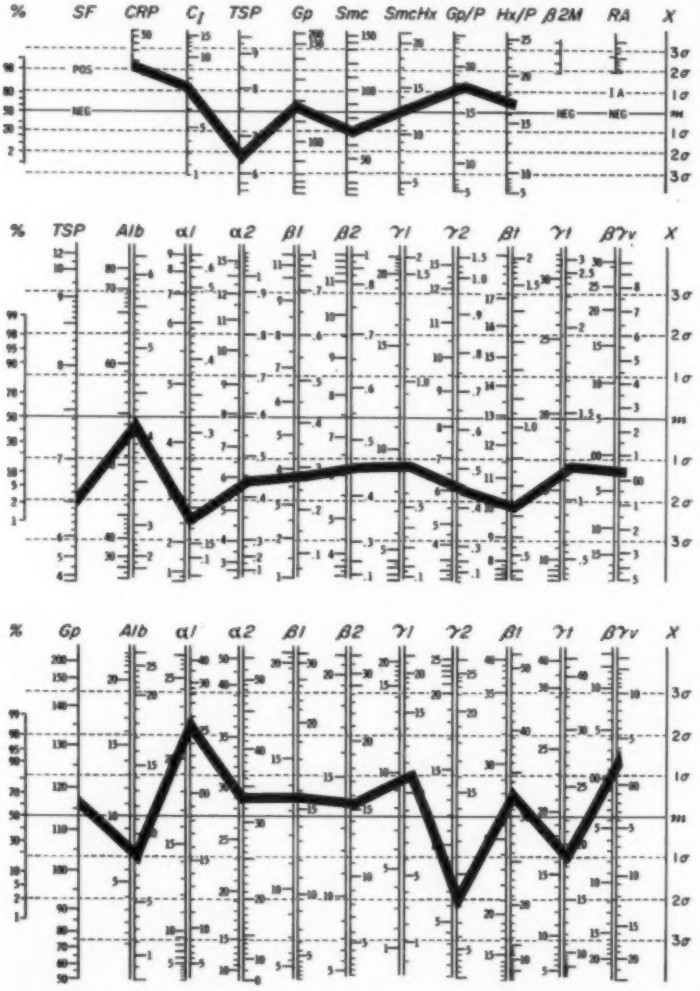

FIGURE 3: Serum protein profile of a patient (No. 2, Table 1) with chronic pulmonary emphysema.

tuberculosis in which it was clinically evident that the probable duration of the disease was longer than that in patient 1.

The SPP was particularly useful in evaluating response to therapy in patients with more than minimal tuberculosis, inasmuch as it could be correlated more closely with disease activity than with anatomic extent of disease as indicated by roentgenographic changes.

The SPP of a patient with moderately advanced pulmonary tuberculosis just beginning chemotherapy showed marked derangement of protein and glycoprotein patterns (Patient 6, Fig. 5) comparable to that of a patient with resistant and far advanced disease (Patient 7, Fig. 6). The serum from a patient with tuberculosis of comparable extent radiographically, but who has responded satisfactorily to therapy, presented

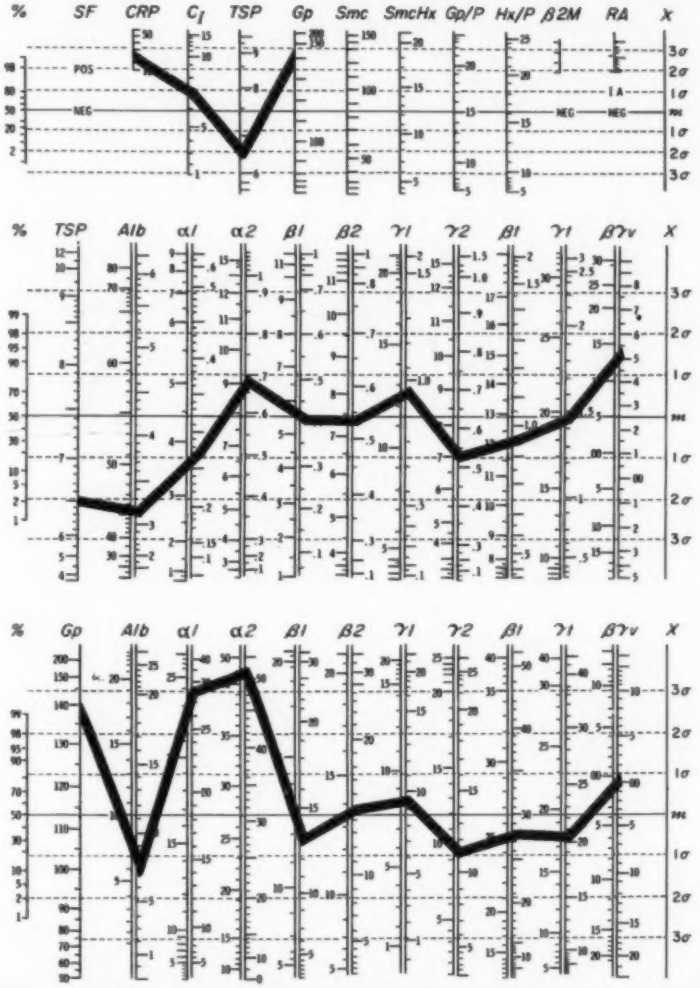

FIGURE 4: Serum protein profile of a patient (No. 5, Table 1) with minimal pulmonary tuberculosis of longer duration than that of patient No. 1 (Fig. 2).

only a slight elevation of alpha-1 glycoprotein (Patient 8, Fig. 7) comparable to that observed in minimal disease (Patient 1, Fig. 2).

During the infection-free phases of recurrent lung infections, such as may occur with a pulmonary cyst, the only abnormality that was observed (Patient 9) was a significant hypergammaglobulinemia of both protein and glycoprotein, possibly due to persistent antibody stimulation by recurrent infection.

A profile characteristic of persistent extensive inflammation with long-continued antigenic stimulation was observed in a patient with disseminated coccidioidomycosis (Patient 10). The serum showed a characteristic alpha-1, alpha-2 glycoprotein increase, alpha-2 protein increase, and marked hypergammaglobulinemia.

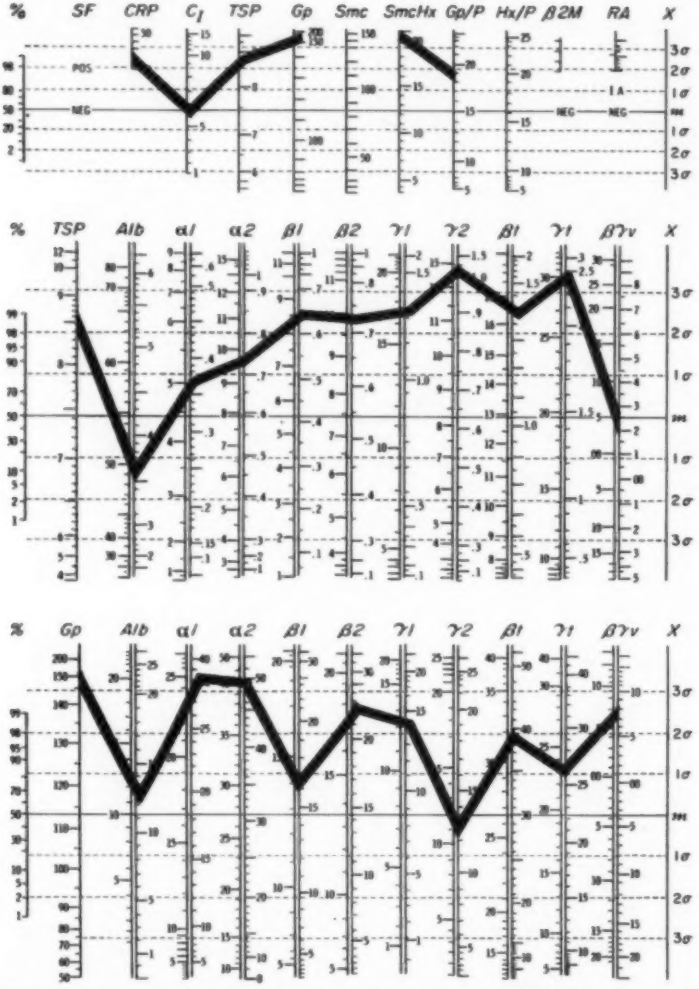

FIGURE 5: Serum protein profile of a patient (No. 6, Table 1) with moderately advanced pulmonary tuberculosis shortly after beginning chemotherapy.

Bronchial asthma has usually been reported to show no significant serum protein abnormality. In our experience, this was true only in uncomplicated allergic asthma during asymptomatic intervals. In serum protein profiles from patients with atypical bronchial asthma, or that which has been termed "intrinsic," a significant but transient alpha-1 (Patient 11, Fig. 8), and in some instances, persistent alpha-2 glycoprotein changes were associated with comparable alpha-1 and alpha-2 protein elevations (Patient 12). It is interesting that patient 11 also showed hypogammaglobulinemia. Although patients with uncomplicated allergic asthma usually have a normal SPP, a significant number on prolonged hyposensitization therapy have been observed to have beta

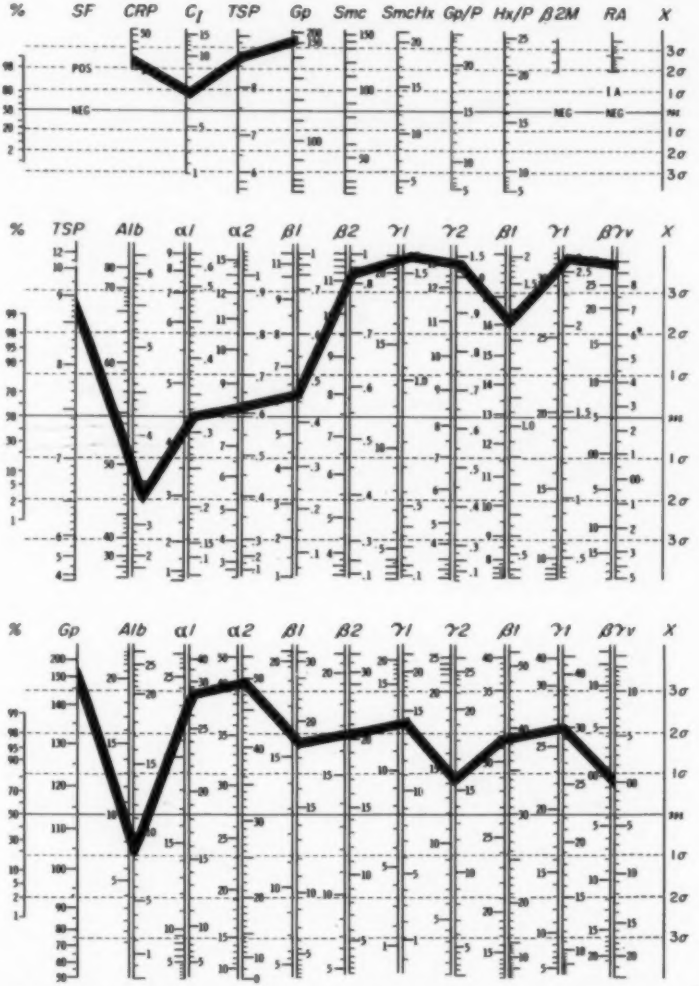

FIGURE 6: Serum protein profile of a patient (No. 7, Table 1) with far-advanced and chemotherapy-resistant pulmonary tuberculosis.

protein and glycoprotein elevations (Patients 12 and 13). Such increases were generally noted in the cathodal half of the beta fraction.

Neoplastic disease of the lung was almost invariably associated with a marked derangement of the SPP. Glycoprotein abnormalities were observed in the early stages and before significant abnormalities of the protein pattern occurred (Patient 14). Most patients in the later phases of the disease also show alpha-1 and alpha-2 protein elevations (Patient 15). The abnormalities observed in the alpha-1 and alpha-2 proteins and glycoproteins were attributed to the inflammatory response resulting from the associated infection. In addition, however, bronchogenic carcinoma was frequently associated with beta-2, gamma-1 glycoprotein elevations (Patients 14 and 15). These have been shown by ultra centri-

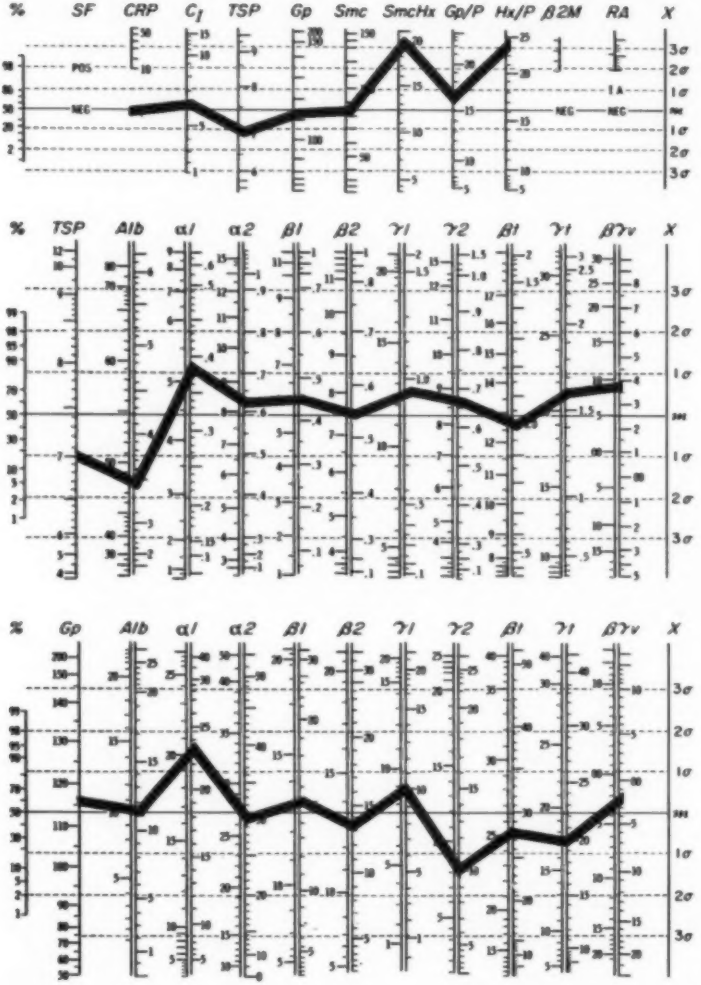

FIGURE 7: Serum protein profile of a patient (No. 8, Table 1) with far-advanced pulmonary tuberculosis who responded satisfactorily to chemotherapy.

fugation and immunoelectrophoresis to be 19 to 22S macroglobulins not present in detectable amounts in normal sera.[7] They are not specific for bronchogenic carcinoma, but also are frequently detected in the sera of patients with rheumatoid disease or with cirrhosis of the liver.

Similar derangement of serum glycoproteins were also observed in Hodgkin's disease (Patient 16), other lymphomata (Patient 17), and other carcinomas (Patient 18). One group of neoplastic diseases, however, is frequently associated with a significant decrease in the gamma proteins. These include lymphosarcoma (Patient 19), lymphatic leukemia (Patient 20), and reticulum cell sarcomas (Patient 21).

As a supplement to paper electrophoresis, dysproteinemic sera were also analyzed immunoelectrophoretically. This was particularly valuable

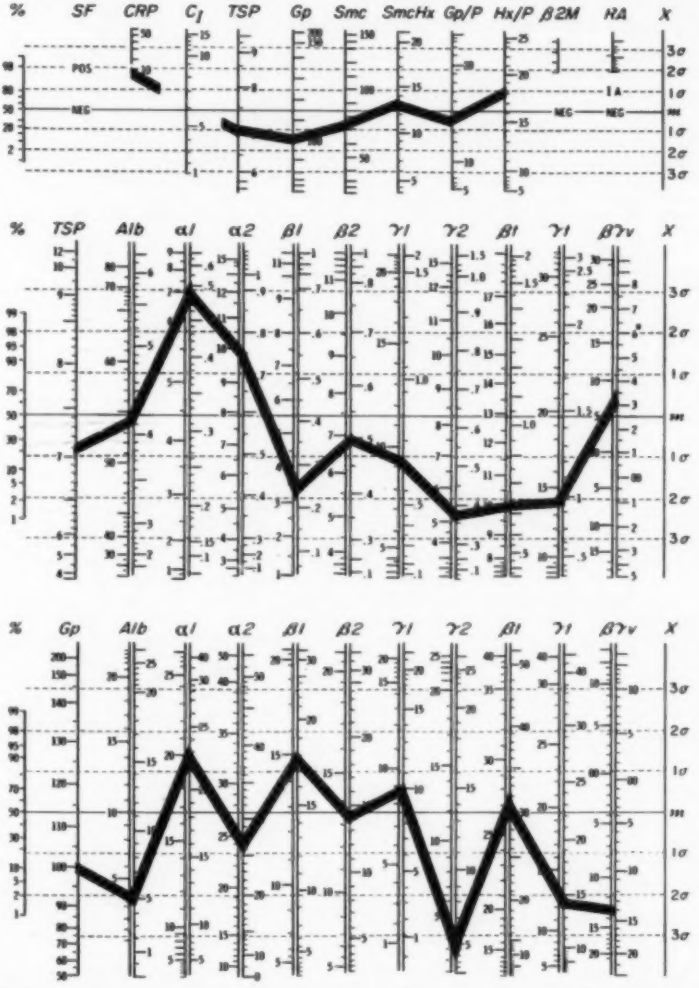

FIGURE 8: Serum protein profile of a patient (No. 11, Table 1) with atypical bronchial asthma.

in distinguishing complete agammaglobulinemia from hypogammaglobulinemia, being sensitive enough to detect as little as 5 mg. per cent of gamma globulin. Patients with levels of gamma globulin low enough to be undetectable on paper electrophoresis still showed a diffuse but perceptable precipitin line in the 7S gamma area on immunoelectrophoresis (Fig. 8). Patients with agammaglobulinemia, however, show a complete absence of the 7S gamma precipitin line.

Discussion

The physiologic and pathologic significance of most of these proteins and glycoproteins is unknown. Although they have been arbitrarily subdivided on the basis of their formation of grossly discrete peaks during electrophoresis, each of the classical fractions has been shown by means of immunoelectrophoresis to be the resultant of several immunologically discrete components (Fig. 9). The alpha-2 protein fraction, for example, consists of at least eight different components. As many as 22 different serum proteins were observed in a pool of pathologic sera.

Some of the components of each fraction have been identified (Fig. 9). Immunoelectrophoresis showed the classic albumin fraction to contain significant amounts of alpha-1 lipoprotein and orosomucoid. The bulk of orosomucoid, which usually comprises the major portion of the seromucoid, moves as an alpha-1 protein along with another inconstantly occurring protein, which from its gel-diffusion characteristics, appears to be a macroglobulin. The alpha-2 fraction contains the low density or so-called beta-lipoprotein believed to be the agent responsible for atherosclerosis.[6] Fusing with and frequently indistinguishable from the lipoprotein arc is the alpha-2 macroglobulin of Schultze, another protein of unknown function. The alpha-2 area also contains caeruloplasmin, or perhaps more than one caeruloplasmin, a copper-containing protein which shows a decrease in certain types of neurologic and liver disease. Haptoglobins also migrate in this area. These are glycoproteins characterized by their ability to combine stochiometrically with hemoglobin and show marked increases in inflammatory and neoplastic disease. They are believed to be responsible, together with fibrinogen, for the observed increase in the erythrocyte sedimentation rate. These proteins show marked decreases in some patients with Laennec's cirrhosis or during intravascular hemolysis.

Most of the proteins of the beta fraction are as yet unidentified. Siderophilin, an iron-containing protein believed to be involved in iron-transport, has been identified as line 11. This area also contains the beta-macroglobulin, which increases to extremely high levels in Waldenström's macroglobulinemia and may be associated with purpura, spontaneous thrombotic phenomena, and cryoglobulinemic phenomena. Although it is not usually observed in detectable amounts in normal sera, increased levels were noted in sera from patients with rheumatoid arthritis, cirrhosis, bronchogenic carcinoma, and psoriasis. It appears to be a protein with very diverse properties, showing in different sera the properties of rheumatoid factor, heterophile antibody, and cold agglutinin. In the ultracentrifuge it sediments in the 19 to 22S fraction.[7] C-reactive protein also migrates in the beta-2, gamma-1 area. Finally, one protein which has been well characterized, and is perhaps the most heterogeneous of all, is

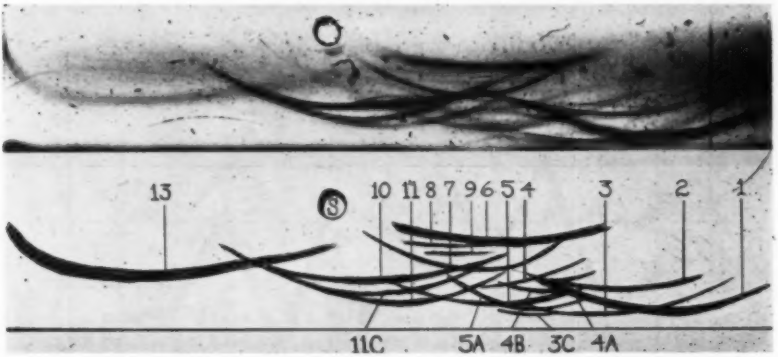

FIGURE 9: Immunoelectrophoretic pattern of a patient with hypogammaglobulinemia. The diffuse precipitin arc (13) indicates very low levels, inasmuch as the gamma globulin arc is ordinarily the most dense in immunoelectrophoretic patterns of normal serum.

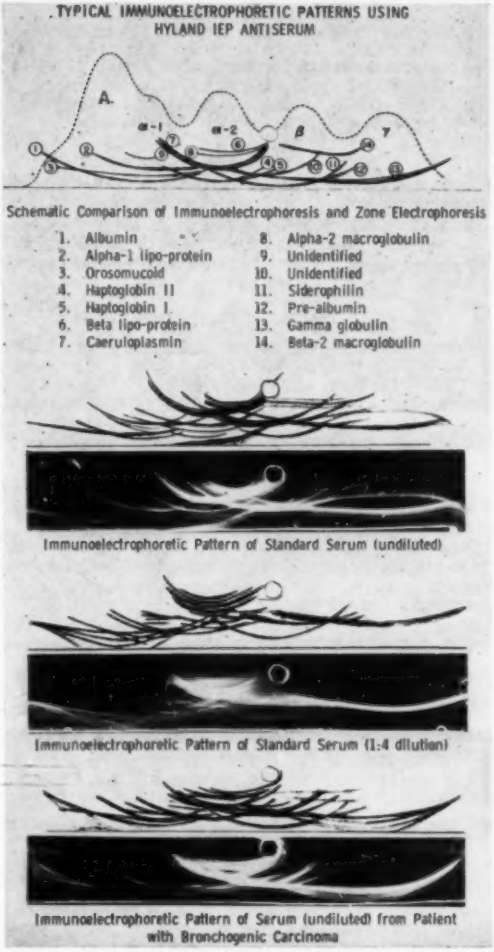

FIGURE 10: Immunoelectrophoretic pattern of serum from a healthy subject. The large number of precipitin arcs, each of which represents an immunologically discrete serum protein, illustrates the complex variables giving rise to the comparatively simple paper electrophoretic pattern.

gamma globulin. Its great physico-chemical heterogeneity parallels its immunologic heterogeneity and is demonstrated by its wide immunoelectrophoretic distribution, extending through both the classical alpha and beta fractions.

It is evident that the changes detectable by paper electrophoretic technique represent only the resultant of many quantitative and possibly qualitative variations of the individual components of each fraction. Studies are currently in progress to develop specific immunochemic techniques for the quantitative determination of these component proteins. With development of more simple quantitative immunochemic techniques, the measurement of these individual proteins may find increased application to clinical chest disease in the near future.

SUMMARY

1. A wide variety of chest diseases is associated with a significant dysproteinemia shown by an abnormal protein profile, (SPP).

2. The glycoprotein pattern is a more sensitive indicator of dysproteinemia than the paper electrophoretic pattern of proteins determined with the BPB stain.

3. The paper electrophoretic patterns are the resultant of various changes of individual components of each fraction.

ACKNOWLEDGMENTS: We are grateful to Dr. Roy T. Fisk, Director of Research, Hyland Laboratories, who generously supplied the immunoelectrophoresis antiserum (IEP, Hyland) used in this study and to the following physicians who provided clinical data on the patients included in this study: Frank W. Ellis, Alfred Goldman, Rachael K. Guth, LeRoy Hyde, Lester Meister, William B. Reed, Samuel E. Reiter, and Kent H. Thayer, Mr. Timothy Dodge, Medical Illustrations Service, Veterans Administration Hospital, Long Beach, provided the illustrations.

RESUMEN

1. Una gran variedad de enfermedades del torax se ascian a una significante disproteinemia segun lo mestra el perfil anormal proteínico (SPP).

2. El cuadro de la gluproteina es sensible indice de disproteinemia que el del papel electroforético en las proteinas determinadas con el colorante BPB.

3. Los cuadros electroforeticos en el papel son resultado de varios cambios de los componentes individuales de cada fracción.

RESUMÉ

1. Un grand nombre d'affections thoraciques sont associées à une nette dysprotéinémie mise en évidence par un tracé protéinique anormal.

2. Le dessin glycoprotéinique est un indicateur plus sensible d'une dysprotéinémie que le tracé électrophorétique des protéines déterminé par la coloration.

3. Les tracés électrophorétiques sont la résultante de différentes altérations des composantes individuelles de chaque fraction.

ZUSAMMENFASSUNG

1. Eine grosse Vielfalt von Lungenerkrankungen geht mit einer deutlichen Dysproteinaemie, erkennbar am krankhaften Serumeiweißbild, einher.

2. Die Untersuchung des Glycoproteins ergibt einen empfindlicheren Hinweis auf eine Dysproteinaemie als die Papierelektrophorese dere Serumeiweißkörper mit BPB.

3. Das papierelektrophoretische Bild ist die Resultante verschiedener Veränderungen individueller Komponenten jeder Fraktion.

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DIFFUSE SPASM AND DIFFUSE MUSCLE HYPERTROPHY OF LOWER ESOPHAGUS

There appears to be two major neuro-muscular disorders of the esophagus—cardiospasms and diffuse spasm of the lower esophagus. Many minor abnormalities such as pseudo-diverticula, rosary, corkscrew esophagus seem to fall into the category of diffuse spasm. From clinical and experimental evidence, there are grounds for suggesting that diffuse spasm is due directly or indirectly to vagal over-activity, but in some instances, inflammatory changes following peptic esophagitis and ulceration may be a casual factor.

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Choice of Initial Chemotherapy Regimen in Pulmonary Tuberculosis*,**

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The title specifically mentions the word "initial" because this is considered the most important part of treatment. It is becoming more obvious that the key to success lies in the first three to six months of therapy. Adequate initial therapy can approach a 100 per cent sputum conversion, whereas inadequate therapy results in many therapeutic failures.

After more than a decade of effective antituberculosis drugs, there is still much disagreement as to what constitutes "adequate chemotherapy." In the past few years, Hughes,[1] Morse,[2] Bell,[3] Middlebrook[4] and others have shown that approximately 30 to 40 per cent of patients are rapid inactivators of isoniazid and achieve inadequate serum isoniazid levels on the standard 300 mg. dosage. This, together with a lack of enthusiasm for the use of daily streptomycin, probably explains the continuing incidence of treatment failures.

The following studies point out the relationship between initial chemotherapy and treatment failures. The first study[5] shows 108 consecutive admissions to National Jewish Hospital, previously treated with combinations of isoniazid, PAS and intermittent streptomycin in conventional doses. These patients were referred to hospital for medical and surgical evaluation (Table 1). Sputum examinations were persistently positive by culture in over 63 per cent of cases, and all but five were drug resistant. A smaller group diagnosed since 1955 is also shown with the various data broken down. In another study (Table 2) 196 patients treated at this hospital with combinations of intermittent streptomycin, isoniazid, PAS, in conventional dosages, were examined. All cases had a follow-up

TABLE 1

Year	Disease Classification			Previous Therapy			Sputum Culture on Admission		Drug Resistance			Drug Susceptibility
	Far Adv.	Mod. Adv.	Min.	Int. SM	INH	PAS	Pos.	Neg.	SM	INH	PAS	
1955	8	6	—	14	14	9	13	1	11	13	5	—
1956	11	14	—	25	21	14	17	8	13	14	4	2
1957	4	3	—	7	6	4	2	5	1	1	1	1
Total	46			46			32	14				

1. One hundred and eight cases admitted consecutively to another hospital since 1956 were studied. In all cases the previous chemotherapy consisted of combinations including intermittent streptomycin.
   On admission, 79 per cent had a positive sputum, and all but five were excreting bacilli resistant to SM and/or INH.
2. In another group, as seen in this table, the chemotherapy in all cases was started (at home or in another hospital) after January, 1955.
   On admission 63 per cent had positive sputum and all but three were drug resistant.

*From District Two State Tuberculosis Hospital.

**Presented at the 26th Annual Meeting, American College of Chest Physicians, Miami Beach, June 8-12, 1960.

TABLE 2—BACTERIOLOGIC STATUS (ALL CASES)

	Admission Sputum		*Final Sputum State		*Failure to Convert per cent	Number of Cases
	Pos.	Neg.	Pos.	Neg.		
Medical	54	14	21	47	38	68
Surgical	77	51	21	107	27	128
	131	65	42	154	32	196

*Represents persistent or intermittent positive secretions, or relapse after a period of negativity.

1. A review of 196 patients discharged between June, 1955 and June, 1956.
2. Conventional therapy (A) intermittent SM with daily INH or PAS (B) INH plus PAS.
3. All patients had long periods of chemotherapy in hospital, the extremes being seven and 29 months.

of two to three years. Sputum failed to convert in approximately 32 per cent of these cases in spite of long chemotherapy and surgery.[6]

A Veterans Administration-Armed Forces report[7] dealing with minimal and moderately-advanced noncavitary cases, and treated with isoniazid or with isoniazid plus PAS, is of interest because even in such select material it fails to show the 99 to 100 per cent sputum conversion achieved with high dosage combinations of drugs in much more critical cases (Table 3). The various trials by the Veterans Administration, United States Public Health, and British Medical Research Council, as seen in Table 4, confirms this important incidence of treatment failures following conventional dosage therapy, which cannot be ignored. Other studies by National Jewish Hospital[8] and Biehl[9] show that even the combination of intermittent streptomycin with high dosage isoniazid fails to prevent the emergence of drug-resistant organisms. Similarly, isoniazid alone or combinations, including cycloserine and pyrazinamide in original treatment cases also show a number of failures.

Material and Method

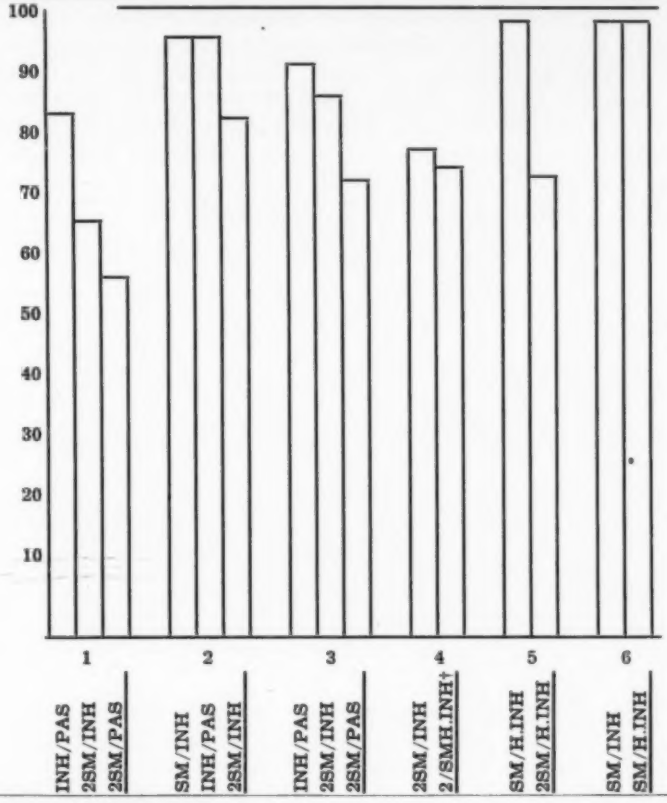
Following November, 1958, patients admitted to our hospital with no previous treatment or less than three months, and with a diagnosis of tuberculosis established by culture, have been placed on a combination of streptomycin 1 gm. daily, isoniazid at least 16 mg./kg. daily with pyridoxine 50 to 100 mg. daily. Sixty consecutive cases who have completed at least six months of treatment are presented here. Drug susceptibility studies carried out in most patients revealed the presence of susceptible bacilli, except in 12 cases where some degree of bacillary resistance was established at time of admission. One of these (Case 60) was resistant to INH, 2 and 5 mcg. per ml., and SM, 2 and 10 mcg. per ml. *in vitro*. PAS was added to the therapy of many of these patients and all converted satisfactorily, except in case 60.

TABLE 3—VETERANS ADMINISTRATION-ARMED FORCES STUDY IN MINIMAL AND MODERATE, NON-CAVITARY DISEASE TREATED WITH INH OR INH PLUS PAS (PERCENTAGE SPUTUM CONVERSION)

	0-4 Months		5-8 Months	
	INH	INH+PAS	INH	INH+PAS
Minimal	65	68	77	95
Moderate Non-Cavitary	67	65	91	81

Streptomycin was given daily usually for about four months. When it was discontinued, PAS was substituted. High INH dosage averaging about 800 to 900 mg. daily was used in each patient because of the lack

TABLE 4—SPUTUM CONVERSION BY FIVE TO EIGHT MONTHS' TREATMENT IN NEWLY DIAGNOSED CASES OF TUBERCULOSIS. VARIOUS DRUG REGIMENS FROM SELECTED SERIES. CONVERSION IN AUTHORS' SERIES WAS OBTAINED BEFORE SIX MONTHS IN ALL CASES.



1. Veterans Administration.
*2. British Medical Research Council.
3. United States Public Health Service.
4. Series by Biehl (vide refs.)
5. National Jewish Hospital, Denver.
6. Authors' Series.

*The patients who continued for six months on SM/INH were more ill on entry to the trial.

†Reproduced from *Acta Tub. Scand.*, 40:2, 1961.

PAS was used in 10 and 20 gm. doses for patients on INH/PAS.

INH/PAS—daily INH with PAS, conventional doses.

SM—daily streptomycin, 1 gm.

2SM—intermittent streptomycin, usually 1 gm. twice weekly, sometimes 3 times weekly.

H.INH—high dosage of isoniazid at least 12 to 16 mgm. per kilo. or higher, given daily in divided doses.

of facilities for serum INH determinations. Seventy-eight per cent of patients had far-advanced disease with extensive cavitation, for example 55 per cent had multiple cavities. Forty-two per cent had cavities with a maximum diameter 5 cm. or greater. Sputum conversion was obtained in 100 per cent by six months of treatment in those cases with a drug susceptible infection originally, and in all but one of the twelve with partial or total drug resistance initially. For the most part, conversion was obtained in the first three months. In a few cases at the beginning of this study, pneumoperitoneum was added after one to three months of therapy in an effort to enhance cavitary closure, but conversion was achieved in all cases without surgery. Toxic symptoms requiring additional measures were observed in about 12 per cent of cases, but in no case was it necessary to discontinue treatment permanently. Moderate to marked x-ray improvement was observed in all but five cases; deterioration in none. Complete cavity closure was not often obtained particularly with cavities more than 4 cm. in diameter.

Discussion

The British trials in the early 1950's[10] established a superiority in the combination consisting of daily streptomycin-isoniazid. Investigators at National Jewish Hospital have confirmed these findings. The early Veterans Administration[11] and United States Public Health Service[12] trials reported best results with daily isoniazid plus PAS. However, all these studies with conventional dosages showed a failure of the sputum to convert with a varying incidence of drug-resistance, in approximately 5 to 42 per cent of cases and subsequent studies have not reported a 100 per cent conversion. Any percentage of failures assumes greater importance if one remembers that trials with other drugs such as pyrazinamide and cycloserine in drug-resistant cases are proving disappointing.

In marked contrast, high dosage regimens in original treatment cases have shown excellent results consistently. Reports from National Jewish Hospital[13] by Berte and associates,[14] from Fitzsimons Army Hospital,[15] as well as our present study, show a sputum conversion in 99 to 100 per cent of cases within six months of treatment irrespective of the extent of disease or cavitation. The Denver group reported two relapses in patients who left the hospital against medical advice within seven months and discontinued all medication. Our study is similar in most respects to that carried out by this group. Berte and associates used one group of patients treated with high isoniazid and PAS, and a second group with daily streptomycin, high isoniazid plus PAS. Sputum conversion and the incidence of toxic reactions were approximately equal in both groups. They suggest that roentgenologic improvement was somewhat better in the streptomycin group.

Thus, we see that adequate chemotherapy in the initial period of treatment can yield excellent results and the number of therapeutic failures is reduced to a minimum. Certainly the rate and rapidity of sputum conversion has so far been unsurpassed. In our opinion, the risks of toxic reactions are not as serious as the risk of failure from the general use of conventional dosage therapy. In the interest of patients, such an opportunity to improve results should not be lightly discarded.

SUMMARY

1. Adequate initial therapy in pulmonary tuberculosis can yield excellent results and the number of failures is reduced to a minimum. In our opinion, the risk of toxic reactions from initial treatment with daily streptomycin in one gm. dosage and isoniazid at least 16 mg. per kg. of body weight, is not as serious as the risk of failure with drug resistance from the general use of conventional dosage therapy.

2. A series of cases treated with such a high dosage regimen is shown. This represents all patients, diagnosed tuberculous by culture and previously untreated, admitted to this hospital after November, 1958 and treated here at least six months. Most of these patients had far-advanced disease with extensive cavitation and sputum conversion was obtained in 100 per cent of those with a drug susceptible infection initialy.

3. The high dosage combination appears to offer definite advantages over the more conventional regimens.

ADDENDUM: Since this paper was submitted, Case 60 had been transferred to another hospital under therapy. Our latest report is that her sputum did convert

culturally in the sixth month of treatment and five consecutive negative cultures were on record. However, an occasional positive smear has been obtained. She has also shown clinical and roentgenologic improvement.

RESUMEN

1. El tratamiento inicial adecuado en tuberculosis pulmonar puede rendir excelentes resultados y el número de fracasos se reduce al mínimo.

Según nuestra opinión el riesgo de reacciones tóxicas debidas al tratamiento inicial con estreptomicina-diaria a la dosis de 1 gmo. y la isoniacida a la de 16 mg. por Kg. de peso al menos, no es tan serio como el riesgo de fracaso por drogorresitencia por el uso de la dosis común.

2. Se presenta una serie de casos tratados con tal régimen elevado.

Esto representa todos los enfermos, diagnosticados de tuberculosis por cultivo y no tratados antes, admitidos a este hospital después de noviembre de 1958 y tratados aquí por lo menos seis meses. La mayoría de estos enfermos tenían tuberculosis muy avanzada con cavernas grandes y la conversión de los esputos se obtuvo en el 100 por ciento.

3. La combinación a dosis alta parece ofrecer ventajas definidas sobre los otros regímenes corrientes.

RESUMÉ

1. Le traitement convenable dès le début de la tuberculose pulmonaire peut apporter d'excellents résultats, et le nombre des échecs est réduit au minimum. Dans l'opinion de l'auteur, le risque de réactions toxiques avec la streptomycine quotidienne à la dose d'un gramme et l'isoniazide à la dose d'au moins 16 mmg. par kilo de poids corporel pour le traitement initial n'est pas aussi grave que le risque d'échec avec résistance aux produits, lorsqu'on emploie le traitement aux doses conventionnelles.

2. L'auteur présente une série de cas traités avec un tel régime de hautes doses. Elle comprend tous les maladese, dont le diagnostic de tuberculose a été fait par cultures, qui n'avaient jamais été traités, hospitalisés après novembre 1948 et traités là pendant au moins six mois. La plupart de ces malades étaient dans un état grave, avec processus cavitaire extensif, et la négativation de l'expectoration fut obtenue dans 100% des cas.

3. L'association à haute dose semble offrir des avantages précis sur les thérapeutiques plus conventionnelles.

ZUSAMMENFASSUNG

1. Eine adëquate initiale Therapie bei Lungentuberkulose kann zu ausgezeichneten Resultaten führen, und die Zahl der Versager wird auf ein Minimum verringert. Nach unserer Meinung ist das Risiko toxischer Reaktionen, die bei einer initialen Behandlung mit täglichen Streptomycingaben von 1 g und INH von wenigstens 16 mg pro Kilogramm Körpergewicht auftreten können, nicht so bedenklich wie das Risiko eines Versagers mit Resistenz infolge allgemeinen Gebrauches der Therapie in den konventionellen Doseirungs-Schema.

2. Es werden eine Reihe von Fällen vorgestellt, die mit einer solchen hohen Dosierungsfolge behandelt worden waren; diese Serie umfaßt alle Patienten, deren Tuberkulose kulturell bestätigt und die zuvor noch nicht behandelt worden waren. Es sind alle Zugänge dieses Krankenhauses seit Nov. 1958 und die mindestens 6 Monate behandelt worden. Die meisten dieser Kranken hatten eine weit fortgeschrittene Tuberkulose mit ausgedehnter Cavernisierung. Sputumkonversion gelang in 100%.

3. Die Kombination in hoher Dosierung scheint eindeutige Vorzüge gegenüber den konventionellen Verordnungs-Schemas zu bieten.

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THORACIC SURGERY IN HIGH ALTITUDE

Three hundred fifteen thoracic surgical interventions were performed at the Chulec General Hospital in Oroya, Peru, located at an altitude of 12,654 feet, in patients of 4 to 66 years of age from August, 1952 to February, 1960. Most of the operations were carried out for pulmonary hydatidosis. This represents 56.5 per cent of all the thoracic surgery in Peru. Tuberculosis was second in frequency for chest surgery. Results were highly satisfactory in patients with lung abscess. Pericardiopleurostomy and pericardial decortication were carried out with gratifying results.

Although the incidence of patent ductus arteriosus in natives from high altitudes was high, surgical complications were substantially reduced by improvement in technic and more flexible techniques of anesthesia and postoperative care. Absence of bronchopneumonias is thought to be due to the fact that because the patient is in an hypoxic environment, he is forced to breathe deeply to cover his oxygen need. After operation, the patients not only inflate their lungs satisfactorily, but also improve the venous return to the heart and prevent peripheral venous stagnation.

Decrease in arterial pressure was observed after major operations, but it was no more frequent or more serious than in institutions located at lower altitudes. Obviously, major surgical interventions may be carried out with safety at high altitudes and recovery is rapid. Patients generally get up on the third or fourth postoperative day.

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Cervicomediastinal Cystic Hygroma*

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Cystic hygroma is a benign loculated tumor of congenital lymphatic origin whose cavities are lined with endothelium. Such tumors are found most commonly in the cervical or axillary regions and less often in the mediastinum, the retroperitoneal area, the inguinal region and the extremities. The descriptive word "hygroma" is derived from the Greek "hygros," meaning moist, and "oma," a tumor.

In 1843, Wernher[1] suggested that cystic hygromas were true neoplasms and not related to developmental anomalies of the fetus, as had been thought previously. Thirty years later, Koester[2] demonstrated an endothelial lining in the cysts of a cervical hygroma and concluded that the cystic cavities were derived from pre-existing lymphatic vessels. It is now generally agreed that cervical hygromas arise from sequestrations of lymphatic tissue derived from the primitive jugular lymph sacs.[3] Controversy remains as to whether these jugular sacs develop by outpocketing of previously laid down venous channels[4] or from mesenchymal deposits,[5] although the first of these views has received more support. The lymphatic rests appear to retain their embryonic power of growth, enabling the cysts to enlarge to considerable size.

Cervicomediastinal cystic hygroma is a rare entity, and we have been able to find only 30 cases reported in the literature.[6-13] It is the purpose of this paper to record nine histologically-proved cases, seven of which have not been reported previously. The treatment with radium of two of the present nine patients was referred to by Figi,[13] and Lemon[14] later reported on these two patients more fully (cases 2 and 3 in this series).

Current Study

Between 1916 and 1959 inclusive, only nine microscopically proved cases of cervicomediastinal cystic hygroma were seen at the Mayo Clinic. Tumors with similar gross characteristics but without microscopic evidence of lymphatic origin were not included in the present series. Of the six surviving patients, one was lost to follow-up. The other five were alive and well 8 to 43 years (average of 17 years) after their last treatment.

The series included five males and four females. The cervical portion of the hygroma was on the right side in six cases and on the left in three. With one exception, all the patients were less than four years of age when first seen at the clinic. The only adult was a 26 year-old woman (Case 6) who first had noticed a mass in the left side of her neck when she was

*Presented at the 26th Annual Meeting, American College of Chest Physicians, Miami Beach, Florida, June 8-12, 1960.

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TABLE 1—PRESENTING CLINICAL FEATURES IN NINE PATIENTS WITH CERVICOMEDIASTINAL CYSTIC HYGROMA

Features		Patients
Swelling in neck		9
Right	6	
Left	3	
Dyspnea		6
Fever		5
Wheezing and stridor		3
Cyanosis		2
Dysphagia		1
Paralysis		1

12 years of age; this was removed 14 years later, and it proved to be a cystic hygroma. A similar tumor was removed from her mediastinum. Within two years, another hygroma appeared on the right side of her neck and also was removed. This is the only instance in the present series in which additional tumor tissue developed.

Table 1 summarizes the presenting clinical features in these nine patients. All of them had a mass in the neck (Fig. 1). In six patients, dyspnea was the most prominent symptom. Fever occurred in five of the nine, but in only one instance was this associated with definite evidence of infection in the tumor. Symptoms of obstruction of the airway were next most frequent, with wheezing, stridor and cyanosis in four patients, two of whom ultimately died. One patient (Case 5) had other developmental anomalies consisting of bilateral clubbed feet and a congenital deformity of the right hand, all of which were subsequently corrected. Dysphagia occurred in one instance, and one patient (Case 8) had paralysis of her right arm from involvement of the brachial plexus by the tumor. In only two instances were the thoracic roentgenograms reported to be normal; in each of these two cases, aspirations of the con-

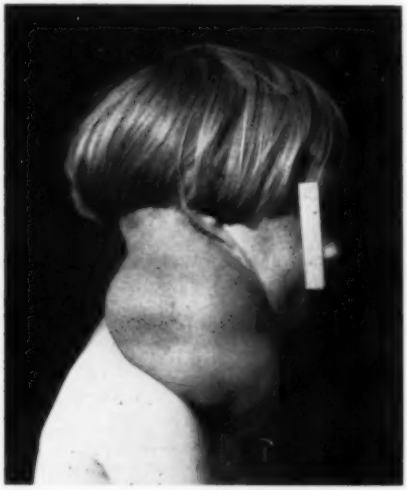

FIGURE 1 (Case 3): Large cystic hygroma extending from posterior triangle of neck to anterior thoracic wall on right side.

tents of the cyst had been carried out before the roentgenologic studies were made. The other seven patients had mediastinal masses at various levels in the thoracic roentgenograms (Fig. 2 and 3). In three of these, a cervical swelling was reported to be present. The tumors usually were extensive and multiloculated, involving at least one side of the neck and the mediastinum. Four patients had projections into the anterior mediastinum, and all of these gave evidence of respiratory obstruction. In three patients, the tumors projected into the pleural cavity.

The basic histologic pattern of these lesions consisted of lymphatic channels and cystic spaces lined with simple endothelium. The walls consisted of fibrous tissue with varying amounts of smooth muscle and occasional lymphocytic infiltration. Other tissues were present depending on the structures involved. The contained fluid was clear or yellowish. Both the gross and microscopic appearance in three of the tumors can be seen in Figures 4 through 7.

Treatment

The results of treatment are summarized in Table 2. The principal treatment in four patients was radium applied to the cervical lesion; two of these also had roentgen therapy to the mediastinum. Two of these four patients died, one from acute respiratory obstruction after the child had returned home and the other from inanition and respiratory obstruction while undergoing treatment. The remaining two patients, one of whom had been given roentgen therapy to the mediastinum, noted reduction in the size of the swelling in the neck but the mediastinal component did not change. In the first patient who died (Case 4), the tumor completely encircled the trachea, compressing it anteroposteriorly. This 15 month-old boy died suddenly at home 5 days after dismissal. He had remained well until a sudden final attack of dyspnea,

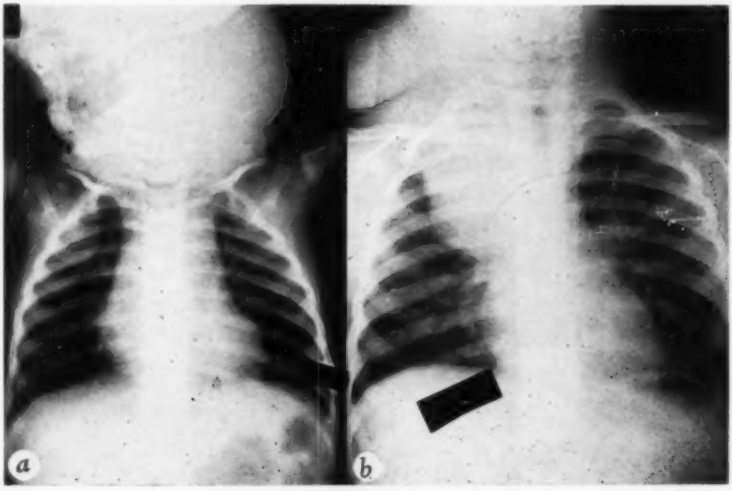

FIGURE 2*a* (Case 2): Superior mediastinal widening (which at this age [10 months] might be attributed wrongly to an enlarged thymus gland) and huge left cervical swelling displacing head and neck to opposite side. FIGURE 2*b* (Case 3): Mass in right superior mediastinum and right side of neck.

TABLE 2—CERVICOMEDIASTINAL CYSTIC HYGROMA: RESULTS IN TREATMENT OF NINE PATIENTS

Treatment	Patients	Persistence or recurrence of tumor	Deaths
Surgical removal	5*	1†	1
Radium or x-ray therapy	4	2	2

*Two patients had radium therapy previously; three had aspiration previously.
†On opposite side of neck.

cyanosis and laryngeal stridor. At necropsy, the fluid in some of the cysts was tinged with blood. The other death was in a 10 month-old infant (Case 2) who had experienced feeding difficulty for 3 months before admission and whose condition steadily worsened during this time. Necropsy disclosed multiple cystic tumors involving the left side of the neck, the larynx, anterior mediastinum and heart. Partial atelectasis was present in both lungs.

Surgical removal was undertaken in five patients. In two of these, radium therapy already had been given, whereas previous aspiration had been performed in the remaining three; in one of the latter patients (Case 1), iodine had been introduced as a sclerosing agent without beneficial effect. Because none of these therapeutic procedures had been successful, surgical removal was undertaken in these five patients, with one operative death.

In three instances, the mediastinal component of the tumor was removed successfully through the incision in the neck. The one adult patient required a two-stage procedure, with removal of the mediastinal component through a left thoracotomy incision after removal of a cystic

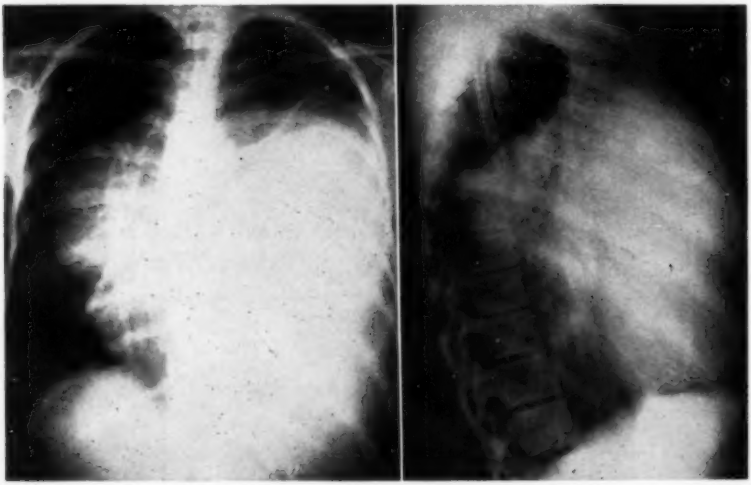

FIGURE 3 (Case 6): Displacement of heart and mediastinum to right side by density filling almost entire left hemithorax. A large circumscribed density can be seen on the right side also. The lateral view shows that the mass is located anteriorly, with superior and posterior extensions.

hygroma from the left side of the neck. This was the patient (Case 6) from whom a similar tumor in the opposite side of her neck was removed two years later.

An axillary hygroma was removed from one patient, but the mediastinal and cervical components were involved so intimately with neighboring structures as to make these lesions inoperable, and roentgen therapy was given instead.

The single operative death (Case 8) was caused by cardiac standstill following hemorrhage; it occurred during removal of the aforementioned cystic hygroma that had infiltrated the adjacent brachial plexus to such an extent as to cause paralysis of the right arm.

The clinical, roentgenologic and therapeutic data in these nine patients are summarized in Table 3.

Comment

When confined to the neck, cystic hygroma is usually asymptomatic. The soft translucent swelling frequently is noticed at birth; it may be only a few centimeters in diameter or it may be almost as big as the child's head. It produces much cosmetic disfigurement and, when large, it may interfere with movement of the head and neck. If initially small, the lesion often enlarges slowly; spontaneous but usually temporary regression has been observed.[15] Although frequently situated in the posterior triangle, it may extend to the axilla or to the floor of the mouth, and it may encircle the neck below the mandibles. The majority of the lesions are noted by the end of the second year of life, with a small number first encountered in later years.[16] Secondary infection occasionally has followed tonsillitis or a respiratory infection, with evidence of sepsis and inflammation in the cyst itself and toxemia that is often profound and may be fatal.

When a mediastinal component is present, symptoms from pressure may develop because of encroachment of the tumor on vital structures in the neck and mediastinum.[14] Dyspnea, wheezing, stridor and cyanosis are caused by pressure on the respiratory passages and have been severe enough to require surgical intervention as an emergency measure to decompress and remove the cyst.[17] Dysphagia, obstruction of the superior vena cava and paralysis of adjacent structures also have been described but are less common. Crying, grunting or any other cause of suddenly increased intrathoracic pressure will produce an increase in the size of the swelling in the neck. Chylothorax and chylopericardium are rare complications[16,19] that did not occur in

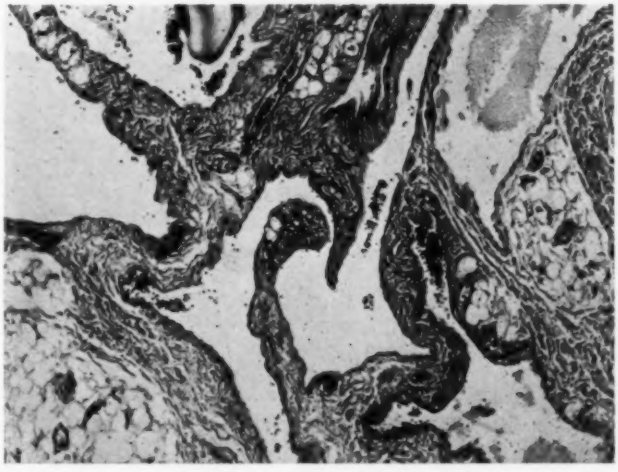

FIGURE 4 (Case 1): Typical cystic hygroma, with spaces that contained lymph. Note the variable smooth muscle in the wall and the focal lymphocytic infiltration in the center (hematoxylin and eosin; x75).

TABLE 3—CLINICAL, ROENTGENOLOGIC AND THERAPEUTIC DATA IN NINE PATIENTS WITH CERVICOMEDIASTINAL CYSTIC HYGROMA

Case	Sex	Age	Presenting features	Duration	Interpretation of thoracic roentgenogram	Treatment	Results
1	M	26 months	Enlarging swelling right neck	2 months	"Negative"	Aspiration and sclerosing agent	Reduced in size
			Swelling recurred, increased rapidly	2 weeks			
			Dyspnea and cyanosis	3 days		Surgical removal	No recurrence
2	M	10 months	Enlarging swelling left neck	From birth	Anterior mediastinal mass	Radium	Death from inanition and respiratory obstruction
			Fever, wheezing, dysphagia, inanition	3 months			
3	F	3 years	Enlarging swelling right neck; occasional fever and dyspnea	From birth	Upper mediastinal tumor	Radium	Reduced in size; enlarged again after whooping cough
		19 years	Swelling right neck			Surgical removal	No recurrence
			Actinodermatitis			Excision	
4	M	15 months	Enlarging swelling right neck	From birth	Upper mediastinal mass	Aspiration and radium, elsewhere; roentgen therapy to mediastinum	Partial relief, with improvement; sudden death from acute respiratory obstruction
			Dyspnea, stridor, cyanosis, fever	3 weeks			
5	M	1 month	Swelling left axilla, right neck; congenital deformities, hands and feet	From birth	Upper mediastinal, right cervical and left axillary masses	Radium	Reduced in size in neck and axilla
		2 years				Removed axillary mass	No recurrence
		3 years				Thoracotomy, inoperable; roentgen therapy	Mediastinum unchanged
6	F	26 years	Enlarging swelling left neck; occasional dyspnea and thoracic pain	14 years	Right hilar mass; left lower thorax opaque	Aspiration elsewhere; surgical removal, two stages	No recurrence
		28 years	Swelling right neck	4 months	"Negative"	Surgical removal	No recurrence
7	M	1 year	Swelling right neck	From birth	Cystic hygroma right neck and upper thorax	Biopsy elsewhere	No recurrence in neck
			Dyspnea and stridor	8 months		Radium	Mediastinum unchanged
8	F	2 weeks	Swelling right neck	From birth	Upper mediastinal and cervical mass	Radium	Reduced in size; mediastinum unchanged
		15 months	Fever, fatigue, listlessness, stiff neck, paralysis of right arm	1 month	Same	Diagnostic aspiration and surgical removal	Death from cardiac arrest at operation
9	F	16 months	Enlarging swelling left neck; fever, redness	2 weeks	"Negative"	Aspiration elsewhere	Reduced in size
		2 years	Swelling recurred; upper respiratory infection	6 weeks		Surgical removal	No recurrence

any of our patients. The association of other congenital defects with cystic hygroma is probably fortuitous; it was noted in only one instance in this group. The majority of patients had the typical features already described.

Roentgenologic examination of the thorax is helpful in demonstrating the presence of a mediastinal mass, often with an associated soft-tissue shadow in the neck. The shape and relative size of the two portions vary with respiration. It does not appear to be worth while to introduce air or contrast medium into the cervical component as a diagnostic measure, especially in view of the great risk of infection and its sequelae, since the diagnosis can be established without this procedure. Cystic hygroma, when present entirely in the mediastinum usually is encountered as an asymptomatic mediastinal mass whose nature is not apparent until thoracotomy is undertaken for diagnosis and treatment. Since it does not possess an extrathoracic component to call attention to itself and because it infrequently compresses vital structures, it may not be found until adult life. It is even rarer than the cervicomediastinal variety.[20]

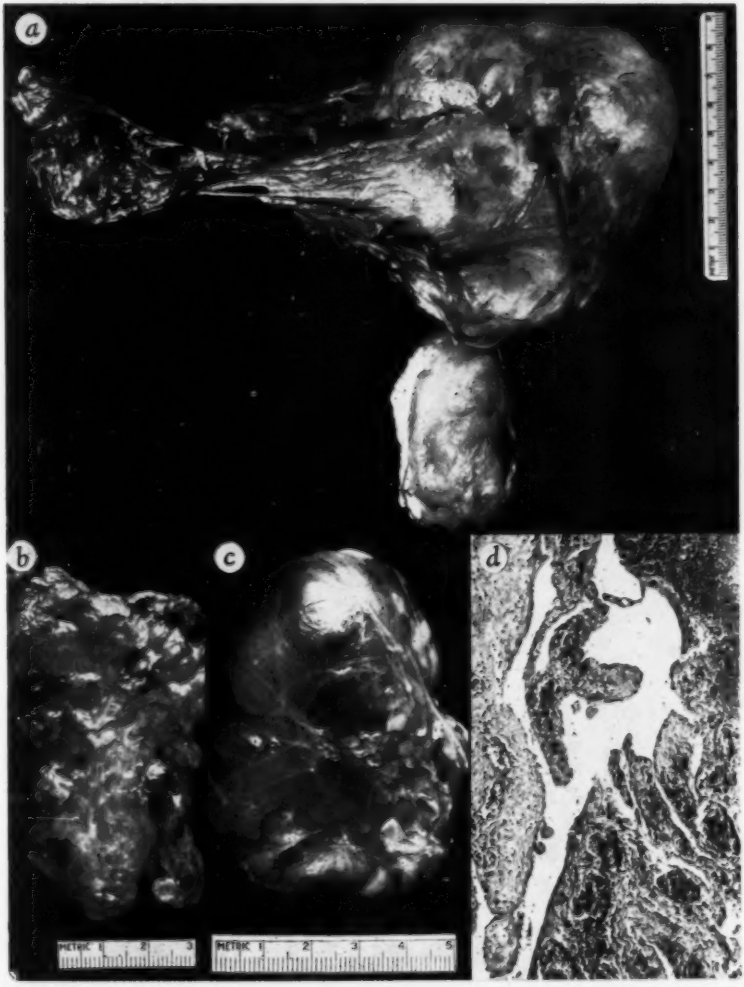

FIGURE 5 (Case 6): Surgical gross specimens. *a*. Large cystic hygroma removed from mediastinum in 1942. *b*. Cystic hygroma removed from left side of neck in 1942. *c*. Cystic hygroma removed from right side of neck in 1944. *d*. Interstitial hemorrhage (upper right) from blood vessels contained in walls and septa of cystic hygroma of mediastinum (hematoxylin and eosin; reduced from X65).

Cysts of apparently lymphatic origin have been described in the parenchyma of the lung. They have occurred as solitary circumscribed lesions amenable to surgical resection[21] and as a more widespread condition, namely congenital lymphangiomatosis of the lung, a polycystic pulmonary disease diffusely involving both lungs.[22]

Cervicomediastinal cystic hygroma forms a large, continuous, loculated and lobulated, cystic mass extending from the neck to the mediastinum. Malignant change has not been reported, but its power of growth and its tendency to compress vital structures in the neck and upper part of the thorax constitute a danger to life. Goetsch[23] was the first to demonstrate the method of growth of these benign tumors. Sprouts of endothelial fibrillar membranes from the walls of marginal cysts penetrate adjacent normal tissues, and lymphlike fluid is secreted within these sprouts. Minute cysts with an endothelial lining form and continue to enlarge. Pressure atrophy of the walls of adjoining cysts occurs, and growth of these tumors is accompanied by destructive action. In this way, large cavities are formed, with fibrillar membranes infiltrating and circumscribing adjacent tissues. Blood vessels and nerves, and the larynx, trachea or esophagus may be completely encircled and compressed. This method of growth accounts for the intimate relationship with surrounding structures and makes it so difficult to remove these tumors completely.

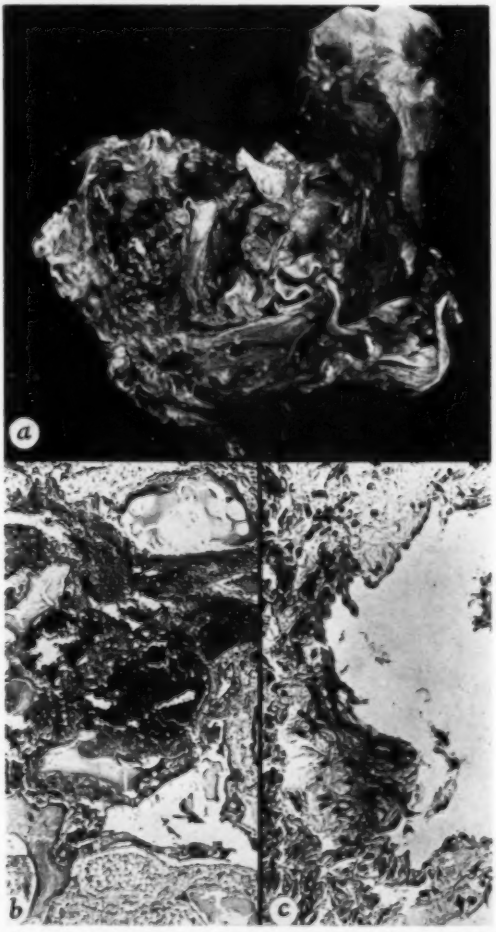

FIGURE 6 (Case 8): *a*. Necropsy specimen from 15 month-old girl, showing hemorrhagic cystic hygroma that encircled and compressed the trachea, esophagus and great vessels (right). *b*. Cystic hygroma infiltrating fibroadipose tissue. Note the blood-filled spaces in center (hematoxylin and eosin; reduced from x30). *c*. Endothelial proliferation (fibrillar membrane) in a cystic hygroma (hematoxylin and eosin; reduced from x180).

The thin-walled cysts are lined with endothelium, and their walls may contain connective tissue, fat, smooth muscle, nerves, blood vessels or lymphoid tissue. The septa between the lobules may be complete or incomplete, and on this depends the freedom of communication of one portion of the tumor with another. The contained fluid is clear or straw-colored; because it is practically free of albumin and globulin, it does not coagulate. Leukocytes of various types, phagocytes, fragmented nuclei and other cellular debris may be centrifuged from the fluid. Cholesterol crystals may be present when previous hemorrhage has occurred within the cyst.

At a time when surgical exploration of the thorax carried with it considerable risk, the treatment of these lesions was restricted to incision and drainage, and possibly the introduction of sclerosing agents, with subsequent application of radium to the cervical component of the tumor. Attempted collapse of the mass by incision and

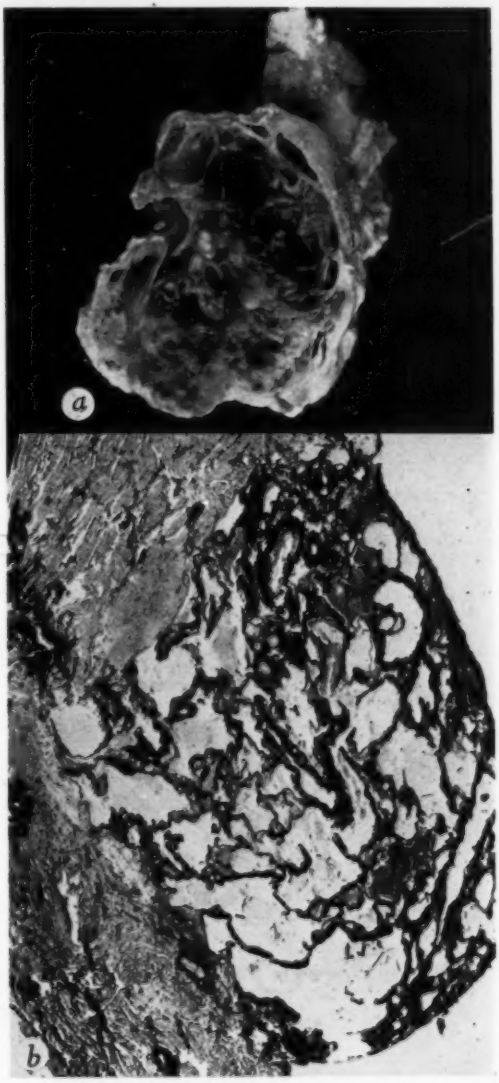

FIGURE 7 (Case 2): *a*. Necropsy specimen of cystic hygroma of left side of neck containing abscess. *b*. Wall of atrium and infiltrating cystic hygroma (right) (hematoxylin and eosin; reduced from x10).

drainage of its contents or obliteration by the introduction of sclerosing agents is likely to fail when there is lack of free communication between the lobules of the cyst because of the septa, which may partition it internally. The danger of infection is also great. Apart from emergency decompression in small children with severe obstruction of the airway, this form of treatment has no place in the present-day management of this condition.

In 1929, Figi[13] reported his results with the use of radium in 12 patients with cystic hygroma of the neck. He did not distinguish those with mediastinal extensions from those without, but he considered that the presence of a mediastinal component made surgical treatment impossible. Six patients experienced either considerable improvement or disappearance of the swelling in the neck, but the remaining six all died from infection of the cyst. He concluded that radium was useful in reducing the size of the tumor to permit surgical removal or in causing its disappearance. He also pointed out the disadvantages of repeated treatment at intervals over a long period, with the possibility of infection developing in the tumor during this time. One of the patients in his series subsequently had recurrence of her tumor after an attack of whooping cough, and this recurrent lesion was removed surgically 15 years later, when she was 19 years of age. At this time, disfiguring radiodermatitis was present, and the affected tissue had to be excised separately.

Others[12,24] have suggested that roentgen therapy has greater advantages, since it is more rapid in its effect, more easily controlled and has sufficient penetration to reach mediastinal lesions, which radium cannot do. Like radium, roentgen therapy will cause complete regression only in some hygromas, while others remain relatively resistant. Roentgen therapy appeared to be of value in one case in our series in controlling the growth of the mediastinal tumor over a period of 17 years, although it failed to make it disappear completely. One other patient has survived without symptoms for 15 years, although no treatment has been given to the mediastinal component of his tumor, which has increased in size only in proportion to body growth. Roentgen therapy is of value when surgical removal is impossible.

Surgical removal offers the only prospect of complete cure. However, because of the infiltrative method of growth of the hygroma, it is often a difficult and tedious procedure, and remnants of the tumor may have to be left behind. Despite this, the rate of recurrence is negligible; local recurrence was absent in this series. However, as noted previously, the one adult patient had an identical tumor on the opposite side of her neck two years after removal of the original hygroma. Remnants of tumor may be treated at the time of operation by sclerosing agents,[17,25] but postoperative roentgen therapy[7,26] and radon seeds[15] have been used with apparently good results.

When possible, the mediastinal component should be removed from the neck along with the cervical tumor, but a separate thoracotomy frequently will be necessary to accomplish this. The operative mortality rate has reached respectable proportions. Of 16 surgically treated patients referred to by Gross and Hurwitt,[6] four died after operation. Since then, five other patients have had surgical removal, with one death.[9-11] Five of our patients were operated on, and one died during the operation. This gives an over-all operative mortality rate of slightly more than 20 per cent, which might be considered extremely high for a benign tumor. However, many of the patients were small children, with considerable inanition, infection and obstruction of the airway. With the use of tracheostomy, antibiotics, better surgical technics and mechanical aids to respiration, there appears to be no reason why this figure cannot be improved greatly. In view of the potential dangers of the tumor, expectant treatment is not justified.

As long ago as 1913, Dowd[3] urged excision as the best treatment for hygromas of the neck. The passage of time has not altered this viewpoint, and the presence of a mediastinal extension renders it more valid. If it should prove impossible to remove the lesion entirely, roentgen therapy is the most satisfactory method for controlling further growth of the tumor.

SUMMARY AND CONCLUSIONS

The clinical, roentgenologic and pathologic features in nine patients with cervicomediastinal cystic hygroma seen at the Mayo Clinic have been presented, bringing the total number of reported cases to 37.

These lesions are congenital tumors of lymphatic origin, and they are loculated and extensive. Despite their histologically benign character, they have an infiltrative type of growth that makes their surgical removal difficult. Malignant degeneration has not been known to occur.

The presence of a cervical mass and the frequent evidence of compression of vital structures in the neck and upper mediastinum cause these lesions to be recognized in the early years of life. They are less common in adults.

Surgical removal is the ideal treatment. When this is not possible, roentgen therapy is effective in some instances in controlling the growth of the tumor.

RESUMEN Y CONCLUSIONES

Se presentan las características clínicas, radiológicas y anatomopatológicas de nueve enfermos de higroma quístico cervicomediastinal, que se han visto en la Clínica Mayo, con lo que el número de casos relatados asciende a 37.

Se trata de tumores congénitos de origen linfático que son loculados y extensos. A pesar de su carácter histológico benigno tienen un carácter infiltrativo de crecimiento que hace su extirpación quirúrgica difícil.

No se sabe que haya habido degeneración maligna de ellos.

La presencia de una masa cervical y la frecuente evidencia de compresión de estructuras vitales del cuello y del mediastino superior, conduce a su descubrimiento temprano en la vida. Es menos común en los adultos.

La resección quirúrgica es el tratamiento ideal, Cuando esto no es posible la roentgenterapia es efectiva en algunos casos controlando el crecimiento del tumor.

RESUMÉ

Les caractéristiques cliniques, radiologiques et anatomo-pathologiques de l'hygroma kystique cervico-médiastinal sont présentées à propos de leur observation chez 9 malades vus à la Clinique Mayo. Ceci porte à 37 le nombre total des cas rapportés.

Ces lésions sont des tumeurs congénitales d'origine lymphatique, et elles sont localisées et extensives. Malgré leur caractère histologiquement bénin, elles sont infiltrantes, ce qui rend leur exérèse chirurgicale difficile. Il n'a pas été constaté de dégénérescence maligne.

La présence d'une masse cervicale et la fréquence d'une compression des éléments vitaux du cou et du médiastin supérieur font que ces lésions sont mises en évidence dès les jeunes années. Elles sont moins communes chez les adultes.

L'éxérèse chirurgicale est le traitement idéal. Quand ce n'est pas possible, le traitement radiologique permet dans certains cas de juguler la croissance de la tumeur.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNG

Bericht über die klinischen, röntgenologischen und pathologischanatomischen Befunde von 9 in der Mayo-Klinik beobachteten Kranken mit cervic-mediastinalen-cystischen Hygromen. Die Gesamtzahl der mitgeteilten Fälle beläuft sich damit auf 37.

Diese Veränderungen entsprechen congenitalen Tumoren lymphatischen Ursprungs, und sie sind gekammert und geräumig. Trotz ihres histologisch gutartigen Charakters besitzen sie einen infiltrativen Wachstumstyp und gestalten dadurch ihre chirurgische Entfernung schwierig. Von einer malignen Entartung ist nichts bekannt.

Das Vorliegen eines Cervical-Tumors und das häufige Vorkommen einer Kompression lebenswichtiger Organe des Halses und des oberen Mediastinums führen dazu, daß diese Veränderungen bereits im frühen Lebensalter bemerkt werden.

Bei Erwachsenen erscheinen sie weniger oft. Chirurgische Beseitigung ist die ideale Behandlung. Wenn dies nicht möglichist, dann ist die Röntgentherapie in manchen Fällen zur Bekämpfung des Tumorwachstums wirksam.

Complete reference list will appear in the reprints.

STUDIES DURING PROLONGED EXTRACORPOREAL CIRCULATION

The decreased levels of the certain blood constituents in the early stages of perfusion appeared to be the results of the proportions of these elements in the patient's blood and in the pooled donor blood used for priming the pump-oxygenator. During the period of perfusion, the following observations were made in a patient who underwent total body perfusion with an artificial pump-oxygenator for over four hours:

The red blood count and hematocrit decreased slightly; the white blood count showed a substantial and progressive increase; the platelet count varied somewhat with the final level showing a slight decrease; the fibrinogen level decreased slightly; the pH showed an early decrease which was corrected by administration of intravenous sodium bicarbonate; evidence was not found for change in peripheral resistance nor expansion in capacity of the vascular bed during perfusion. With quantitative aspiration of blood loss in the operative field, it was not necessary to add blood beyond the original priming volume of the pump-oxygenator; the active heparin level decreased rapidly during perfusion, necessitating periodic infusion of additional amounts of heparin to prevent clotting in the system; addition to protamine to the blood at the end of perfusion produced satisfactory blood coagulation. Clot retraction was normal and there was no evidence of fibrinolytic activity; free plasma hemoglobin did not increase to dangerous levels, despite the prolonged use of the blood aspirator.

Andersen, M. N.: "Studies during Prolonged Extracorporeal Circulation," *J. Thor. and Cardiol Surg.*, 41: 244, 1961.

The Rehabilitation of Chronic, Drug Resistant Cases of Tuberculosis with Cycloserine, and Successful Treatment of Virgin Cases*

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Cycloserine (CS) was introduced as an antituberculosis drug about five years ago.[1,2] Since its introduction, we have used it alone or in combination with other agents in the treatment of over 450 cases of pulmonary and other types of tuberculosis at Metropolitan Hospital in New York City. We found its effectiveness against tuberculosis which had become resistant to other drugs most encouraging, and feel that CS has been instrumental in salvaging many of our hopeless cases.

The published material on CS is much too voluminous to mention here. Suffice it to say that in addition to our own work with the drug, various phases of which have been published from time to time, many others throughout the United States, and indeed throughout the world, have used CS as an antituberculosis agent, with a good degree of success.

Besides being an antituberculosis drug, CS is also an effective broad-spectrum antibiotic.[3-6] Lillick, *et al.*[3] found it effective in the treatment of various systemic infections due to nonspecific organisms susceptible to it. Cycloserine is highly water soluble and has been found in all the secretions and tissues in which it has been sought, including spinal and amniotic fluid, mother's milk, placental and fetal blood of parturient patients, and in the sputum of tuberculosis subjects.[6,7] It is excreted into the urine in high concentrations,[4] thus becoming effective treatment in genito-urinary infections due to CS-susceptible organisms.[4] It is effective in donovanosis,[6] but impotent against gonococcal infections,[4,6] and lymphogranuloma venereum.[4]

The data reported herein were obtained on 397 patients (296 men and 101 women) ranging in age from 13 to 84 years. All were treated for a minimum of six weeks, and 175 were treated for one year or longer. At the start of CS therapy, more than half of the patients had caseopneumonic tuberculosis of relatively recent origin. There were three cases of miliary tuberculosis.

The patients were assigned to certain groups, depending on their clinical status and type of therapy (Table 1), and studied as part of a continuing research project. Other subjects were treated in the wards or outpatient department of the hospital on a routine basis when CS became available commercially, but these are not included in this report.

Prior to CS administration, and in addition to the studies incident to the tuberculous process, all patients were subjected to complete blood studies, liver and kidney function tests, urinalysis, and detailed x-ray film study of the anatomic condition of the lungs. Sputum volume was

*Presented at the 26th Annual Meeting, American College of Chest Physicians, Miami Beach, June 8-12, 1960.

measured and a Gaffky count of tubercle bacilli estimated. The bacilli were cultured periodically and their sensitivity to INH, PAS, streptomycin, and CS was determined according to the methods recommended by the National Tuberculosis Association. Plasma level determinations were made on all but eight of the subjects who are included in this report. Occasionally, the presence of CS was determined in the sputum and urine, as well as in other body fluids.[6]

It has been ascertained that CS plasma levels after oral dosing cannot be predicted, but must be determined by chemical assay.[10] We have shown that on the basis of individual patients, the plasma level is closely related to the dose when it is based on the body weight. That is, a doubling of the CS dose in mg./Kg. will about double the plasma level in mcg./ml.[11]

In a group of 17 subjects in whom the oral dose of CS was from 8 to 22 mg./Kg., the plasma levels ranged from a low of 7 to a high of 48 mcg./ml. It was our observation that most subjects who had plasma levels of 20 mcg./ml. or less did not respond as satisfactorily to the antimicrobial effects of CS as those with consistently higher levels.

It was also demonstrated that the CS plasma level could be used as an index of impending neurotoxicity.[10] This supported our contention that administration of the total daily dose of CS should be made in divided doses.[12,13] Keeping the unit dose as small as possible virtually eliminated the excessive daily peaks of plasma levels, which were associated with the appearance of toxic reactions. In our experience, a CS plasma level of 20 to 50 mcg./ml. was the "ideal" therapeutic range.[10,13] Toxic reactions were most frequent in cases with plasma levels exceeding 50 mcg./ml.; they were rarely seen in patients whose levels were below this.

In addition, we found that pyridoxine administered during CS therapy prevented the more severe neurotoxic reactions and reduced the incidence of tremors and lesser toxic manifestations.[10,14] Therefore, the concomitant administration of pyridoxine in stubborn or regressive cases allows an increase in CS dosage, with a minimum risk of toxic reactions.

Treatment of Drug Resistant Cases

Proof that CS was effective in the treatment of tuberculous infections in man and that tubercle bacilli which had become resistant to INH, PAS, and streptomycin retained their sensitivity to CS[15] afforded a means for the successful treatment of the increasing number of resistant

TABLE 1—CYCLOSERINE THERAPY: SUMMARY OF ALL SUBJECTS

Treatment	No. Cases	Dose - Gm./Day CS	INH	Clinical Status
CS Alone	44	0.5 - 2.0	—	Original
CS Alone	114	0.5 - 2.0	—	Drug Resistant
Total	158			
CS-INH	183	0.5	0.3	Original
CS-INH	21	1.0	0.3	Original
CS-INH	10	1.0	0.6	Original
CS-INH	25	1.0	0.3	Drug Resistant
Total	239			
Grand Total	397			

infections accumulating in our hospital. A first report on 29 such "hopeless," far-advanced, cavitary cases was made in 1955.[1] Since then, we have treated a total of 139 subjects with drug-resistant infection, 114 with CS alone, and 25 with a combination of CS and INH.

All the patients covered in this study had been on our wards for many years and were doomed to remain there. Their x-ray films showed far-advanced, fibrotic, and destructive lesions which had not changed much under previous therapy. Since fibrotic and cavity-ridden lungs cannot be reconstituted, x-ray films could not be used as a criterion for the effectiveness of CS treatment.[16] We felt that any type of improvement in their clinical picture, such as a lowering in the infectivity of the sputum or a lessening in the degree of cough, would be a change for the better in these subjects.

Data on 106 retreatment subjects who received CS alone are summarized in Table 2. Within two months, 15 patients who had been bedridden prior to the start of CS therapy became ambulatory. All had gained in weight, ate better, were consistently afebrile, and had a brighter outlook on things in general. Within six months after the start of CS therapy, 27 patients left the hospital, often against our advice, because they felt better. In 56 subjects who were treated for at least one year, there was sputum conversion in 22, who were rehabilitated sufficiently to leave the hospital and to be employed gainfully. The poor x-ray film showing of many of these cases re-emphasizes the fact that fibrotic and cavity-ridden lungs cannot be reconstituted.

Table 2 also shows data on 27 subjects who had received 2.0 Gm. of CS daily, with 300 mg. of pyridoxine hydrochloride, as a special project for the demonstration of the protective action of pyridoxine on the toxic effects of CS. Although the number of subjects is relatively small, we believe that the larger dose of CS resulted in a greater improvement in a shorter time. The low incidence of toxicity as related to the plasma levels of these 27 subjects has been reported elsewhere.[19]

Cycloserine combined with INH was given to 25 subjects with drug-resistant tuberculosis. They had been receiving INH and PAS for many months with no sign of clinical or objective improvement. The INH therapy was retained because some patients regressed when the drug

TABLE 2—CYCLOSERINE THERAPY: RETREATMENT OF DRUG RESISTANT CASES

CS Dose Gm./Day	Age	Sex		Pre-therapy Status*		During Therapy Sputum Neg. Months†		During Therapy X-ray Impr. Months	
		M	F	MA	FA	6	12	6	12
1.0-1.5	48 (24-77)	62	17	9	70	21/63	17/47	8/63	7/47
		Percentile Improvement				33	28	13	15
2.0	46 (23-61)	23	4	2	25	10/16	5/9	2/16	3/9
		Percentile Improvement				63	55	13	33
Totals	47	85	21	11	95	31/79	22/56	10/79	10/56
	Combined Percentile Improvement					39	39	15	18

*MA=Moderately advanced; FA= Far advanced.

†Fractions indicate total number in the denominator and improved subjects in the numerator.

TABLE 3—CS-INH THERAPY: 214 VIRGIN CASES
CHRONOLOGICAL CHANGES IN X-RAY FILMS

Degree of Change	Months of Treatment 2	4	9	12	over 12
Marked Improvement	3	31	69	49	30
Moderate Improvement	85	112	87	22	14
Slight to None	121	44	11	0	0
Worse	5	4	0	4	0
TOTAL	214	191	167	75	44

was removed, and we believed that the INH was exerting a delaying action on the growth of the tubercle bacilli, despite the fact that the patients were resistant to the drug. The results with 1.0 Gm. of CS and 0.3 or 0.6 Gm. of INH daily do not differ in any way from those shown in Table 2, where 1.0 to 1.5 Gm. of CS alone was administered. Similar results have been obtained by others using CS in drug resistant, "salvage" cases.[17,18]

Treatment of Virgin Cases

Treatment of virgin cases of pulmonary tuberculosis with CS included 44 subjects who received from 0.5 to 2.0 Gm. of CS daily as the only form of treatment, and 214 who received CS in combination with INH, as shown in Table 1.

Laboratory data had revealed an additive and possibly synergistic effect between CS and INH. This suggested to us that CS could be combined with INH in the treatment of virgin cases.[15] We felt that the combination of CS and INH might destroy the tubercle bacilli before resistance to INH could develop. Even if resistance to INH did develop,[16] CS would continue to be effective because resistance to CS, when it is seen, develops slowly and to a slight degree.

Prior to the start of CS therapy, examination of the patients showed the majority to have cough, fever, a history of weight loss, and profuse sputum which was strongly positive for tubercle bacilli. X-ray films revealed cavitation in the lungs of more than two-thirds of these 258 patients. Table 3 shows the degree of change in the lungs as estimated from the x-ray films. Of the 75 subjects who were treated for a full year, 71, or 95 per cent, showed marked to moderate improvement. Sputum conversion followed a course parallel with the clinical improvement and the x-ray film estimate of the pulmonary involvement.

TABLE 4—CS-INH THERAPY: 191 VIRGIN CASES
CHRONOLOGICAL CHANGES IN SPUTUM INFECTIVITY

Status of Sputum*	Months of Treatment 2	4	9	12	over 12
Negative	84	114	83	35	20
Positive on Smear	86	26	20	13	7
Positive on Culture Only	21	29	32	14	9
TOTAL	191	169	135	62	36

*Initially, all sputa were strongly positive on smear and culture.

The data summarized in Table 4 show that after two months of combined therapy, the sputa of only 84 of 191 (44 per cent) subjects tested had become negative to smear and culture for tubercle bacilli. However, at this time the sputa of all patients were reduced in volume, cough had lessened markedly, and the number of estimated bacilli per unit volume of sputum had diminished. After four months of treatment, 114 of 169 sputa, or 67 per cent, had become negative to smear and culture. Of 62 subjects remaining at the end of one year, 34 (56 per cent) were negative, with an additional 14 (23 per cent) positive to culture only. These results compare favorably with those obtained after the use of INH-PAS therapy in similar cases.

Table 5 shows the CS plasma levels obtained using CS-INH therapy. The plasma levels of the 164 subjects who received 0.5 Gm. of CS and 0.3 Gm. of INH daily averaged 12.5 mcg./ml.; those from 36 subjects who received 1.0 Gm. of CS and 0.3 or 0.6 Gm. of INH daily averaged 26.9 mcg./ml. These values are comparable to those seen after the use of CS alone.

The clinical efficacy of CS alone in previously untreated patients with advanced, cavitary tuberculosis is illustrated by the data from a group of 16 subjects. These subjects, ten with far advanced and six with moderately advanced tuberculosis, received increasing doses of CS, starting with 0.5 Gm./day, until the plasma levels were between 30 and 50 mcg./ml., where they were maintained with a daily dose of from 1.0 to 2.0 Gm. given in four divided doses. There resulted a prompt and sustained gain in weight and conversion of the sputum.

After 6 to 12 weeks of treatment, only six of the 16 subjects had sputa positive for tubercle bacilli, three to culture only. In all cases, the sputum volume had been reduced and cough was virtually absent, making it difficult to obtain a sufficient amount for smear and culture. Gastric washings were used in all cases where the sputum was negative. At our hospital, the 74 per cent sputum conversion within 24 weeks of treatment is considered to be as good a result as we have obtained with other drug regimens in equally severe cases.

After 12 weeks of treatment, clinical progress as gauged by x-ray film was classified as slight in one, moderate in nine, and marked in five. One was reported as worsening, despite the fact that his initial, highly positive sputum had become negative to smear and culture of gastric washings, and he had gained 28 lb. in weight, after 24 weeks of CS therapy. His plasma levels averaged 43 mcg./ml. from the 1.0 Gm. per day dose of CS. Ten of the 16 patients had temperatures of from 100 to 104°F. at the onset of treatment, all of which became normal within four to six weeks of therapy.

TABLE 5—CS-INH THERAPY: PLASMA LEVELS

Group	No. Cases	Therapy - Gm./Day		CS Plasma Levels mcg./ml.	
		CS	INH	Average	Range
1	164	0.5	0.3	12.5	2-35
2	36	1.0	0.3-0.6	26.9	9-48

SUMMARY

1. Data are presented on 397 cases of tuberculosis treated with cycloserine (CS) alone, or in combination with INH. The original purpose of combining CS and INH was to obtain a CS dose which would enhance the antituberculosis effects of INH, while keeping the toxicity at a minimum.

2. Our data show that the therapeutic efficacy of CS, alone or combined with INH, depends upon the attainment and maintenance of CS plasma levels above 20 mcg./ml.

3. The toxicity of CS has been reduced,

a) by the concomitant administration of pyridoxine hydrochloride, which also protects against INH in combination therapy;

b) by spreading the daily dose as widely as possible, and

c) by insuring that the plasma levels of CS are kept well below 50 mcg./ml.

Under this regimen, very few cases had to be discontinued because of toxicity.

4. Cycloserine alone in doses which maintain the plasma level at about 30 mcg./ml. has been shown to induce prompt clinical and roentgenographic improvement, a gain in weight, and rapid reversal of infectiousness, in a large proportion of both resistant and virgin cases of tuberculosis.

5. Bacillary resistance to CS developed but rarely, and in our experience has never been complete, even after continuous administration over several years.

ACKNOWLEDGMENT: The cycloserine used for this study was supplied by Eli Lilly and Company as Seromycin. The CS-INH combination capsules were also obtained through Eli Lilly.

RESUMEN

1. Se presenta la información sobre 397 casos de tuberculosis tratados con cicloserina (CS) sola o en combinación con INH.

El propósito original para combinar cicloserina y la INH fué obtener una dosis de CS que aumentase los efectos antituberculosos de la isoniacida mientras se conservaba una toxicidad mínima.

2. Nuestros datos muestran que la eficacia terapéutica de la CS sola o combinada con INH depende de que se alcance y mantenga un nivel de CS en el plasma arriba de 20 mcg./ml.

3. La toxicidad de la CS se ha reducido por:

a) El uso concomitante de clorhidrato de piridoxina que también proteje contra la INH en la comibación;

b) la dispersión de la dosis diaria tanto como sea posible y

c) asegurándose de que el nivel en el plasma se mantenga bien abajo de 50 mcg./ml.

Bajo este régimen muy pocos casos han requerido la suspensión del tratamiento por la toxicidad. La cicloserina sola en dosis que mantenga el nivel en el plasma alrededor de 30 mcg./ml. ha demostrado que produce mejoría clínica y radiológica, aumento de peso y rápida desaparición de la infecciosidad en gran proporción de casos ya sean resistentes o casos no tratados previamente te, de tuberculosis.

5. La resistencia bacilar a la CS se presentó pero rara vez y según nuestra experiencia nunca ha sido completa aún después de interrupción de la administración por various años.

RESUMÉ

1. L'auteur présente ses conclusions sur 397 cas de tuberculose traités par la cyclosérine et l'isoniazide l'auteur s'était primitivement proposé d'obtenir une dose de cyclosérine qui renforcerait les effets antituberculeux de l'isoniazide, tandis qu'elle aurait une toxicité réduite au minimum.

2. Ses constatations montrent que l'efficacité thérapeutique de la cyclosérine, seule ou associée à l'isoniazide, dépend du fait qu'on puisse atteindre et maintenir des taux de cyclosérine dans le plasma au-desus de 20 mg./ml.

3. La toxicité de la cyclosérine a été réduite:

a) par l'administration simultanée d'hydrochloride de pyridoxine, qui protège également contre l'isoniazide dans l'association thérapeutique;

b) en distribuant la dose quotidienne en autant de prises que possible;

c) et en s'assurant que les taux dans le plasma de la cyclosérine sont bien endessous de 50 mg./ml.

Avec cette posologie on ne dut arrêter le traitement à cause de la toxicité que dans un très petit nombre de cas.

4. La cyclosérine seule, à des doses qui maintiennent le taux plasmatique aux environs de 30 mmg./ml. se révèle capable de produire une amélioration rapide clinique et radiologique, un gain de poids, et une sédation rapide de la maladie, dans une grande proportion de cas de tuberculose aussi bien resistants que traités pour la première fois.

5. Une résistance bacillaire à la cyclosérine a pu se développer mais de façon rare, et dans l'expérience de l'auteur, n'a jamais été totale, même après administration continue pendant plusieurs années.

ZUSAMMENFASSUNG

1. Es wird das Zahlenmaterial vorgelegt von 397 Fällen von Tuberkulosen, die mit Cykloserine (CS) allein oder in Kombination mit INH behandelt wurden. Die ursprüngliche Absicht der Kombination von CS und INH war, zu einer CS-Dosis zu kommen, melche die antituberkulöse Wirkung von INH steigerte und die Toxizität gleichzeitig auf einer niedrigen Höhe hielt.

2. Unsere Ergebnisse zeigen, daß die therapeutische Wirksamkeit von CS, sei es allein oder in Verbindung mit INH, abhängt von der Erreichung und Aufrechterhaltung von CS-Plasma-Werten von mehr als 20 Mikrogramm pro Kubikzentimeter.

3. Die Toxizität von CS ließ sich verringern durch:
a) die gleichzeitige Verabfolgung von Pyridoxin-Hydrochlorid, das auch gegen INH bei der Kombinationstherapie eine Schutzwirkung hat;
b) die Verteilung der Tagesdosis, soweit wie irgend möglich, auf verschiedene Stunden und
c) die Sicherstellung, daß die CS-Plasma-Werte eindeutig unter 50 Mikrogramm pro Kubikzentimeter bleiben.

Bei einem solchen Vorgehen erfahren sehr wenig Fälle eine Unterbrechung wegen Toxizität.

4. Cykloserin allein in einer Dosierung, melche die Plasmawerte bei ungefähr 30 Mikrogramm pro Kubikzentimeter erhält, führte nachweislich zu einer raschen klinischen und röntgenologischen Besserung, einem Gewichtsanstieg, einer schnellen Behebung der Ansteckungsfähigkeit bei einer großen Fallzahl, sowohl resistenter, als auch unbehandelter Tuberkulosen.

5. Es kam wohl zu einer bazillären Resistenz gegen CS, aber sehr selten, und sie war auch nach unseren Erfahrungen niemals vollständig, selbst nach über mehrere Jahre fortgesetzter Anwendung.

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PERINATAL DISTRESS SYNDROME

Pulmonary hemorrhage in the newborn may occur in small, clinically insignificant amounts or may at times be massive, resulting in rapid demise. Fetal anoxia is probably the most probable cause, although this may be complicated by hypothrombinemia or hemorrhagic disease of the newborn. Pulmonary hemorrhage frequently accompanies fatal erythroblastosis fetalis. No clinical findings may be limited to respiratory distress or, in the severe cases, there may be hematemesis or the passage of large amounts of forthy blood from the nose and mouth. Radiographs of the chest show linear and patchy areas of increased density, usually in both lungs, and the prominence of the markings and the distribution depend upon the severity of the intra–alveolar hemorrhages.

Singleton, E. B., Rosenberg, H.M., and Samper, L.: "Radiologic Considerations of the Perinatal Distress Syndrome," *Radiology*, 76:200, 1961.

SPONTANEOUS CLOSURES OF VENTRICULAR SEPTAL DEFECTS

A group of 37 children is described in whom a systolic murmur heard early in life gradually diminshed and eventually disappeared. When the patients were first seen, the clinical findings suggested a small ventricular septal defect but no thrill was present and the systolic murmur had a superficial blowing quality with high-frequency vibrations and tended to stop before the second heart sound. Cardiac catheterization demonstrated a small left-to-right shunt at ventricular level in four of the patients while the murmur was present; in one, this was repeated after the murmur had gone and no abnormality could be demonstrated.

Cardiac catheterization in other patients with typical disappearing systolic murmurs showed a left-to-right shunt in some, but in others, this was too small to be detected by routine oxygen studies. With angiocardiography and intracardiac phonocardiography, the exact site of the ventricular septal defect was localized to the muscular portion of the septum in four of the patients.

In one patient who presented with congestive heart failure, clinical and hemodynamic findings of a large ventricular septal defect disappeared. Children with the specific type of systolic murmur described may be recognized as having a small defect in the muscular ventricular septum. The defect is thought to be gradually reduced in size and ultimately closed by hypertrophy of septal muscle. Spontaneous closure appear to be not uncommon with small ventricular septal defects and may occur rarely with lesions large enough to present with congestive heart failure.

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The Acute Effect of Cigarette Smoking on Pulmonary Function Studies*

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This study was undertaken to determine the immediate effect of cigarette smoking on ventilatory studies in both normal individuals and in patients with pulmonary disease.

Previous studies by Juurup and Muido[1] and by Bickerman and Barach[2] had failed to detect significant changes in pulmonary function after smoking. However, Motley and Kuzman[3] found a decrease in compliance immediately after smoking in both normal subjects, and in those with pulmonary disease, and increased airway resistance was reported by Eich[4] in patients with emphysema. Attinger, Goldstein and Segal[5] observed an increase in mechanical resistance and work of breathing in patients with emphysema after smoking two cigarettes.

Material and Methods

The group with pulmonary disease consisted of 23 patients and included all who were hospitalized for pulmonary disorders in the three months preceding the completion of the study. The youngest was 35 and the oldest 81, with a median of 59 years. There were 20 men and three women. Their conditions included emphysema, bronchiectasis, tuberculosis, bronchogenic carcinoma, sarcoidosis and silicosis. The degree of pulmonary dysfunction was considered severe in 11, moderate in six and minimal in six (Table 1).

The normal group consisted of 19 house physicians and other hospital personnel who volunteered for the study. There were 17 men and two women. They ranged in age from 20 to 54 years with a median of 30 years. All had been smoking 10 to 40 cigarettes per day for a minimum of two years. Each was normal on physical examination and had a normal chest roentgenogram taken within six months of the study (Table 2).

All ventilatory studies were performed on a closed-circuit Godart double spirometer.[6] One bell serves to replace continuously the oxygen consumed by the subject from the other so that straight-line graphs of pulmonary ventilation are obtained.

The timed vital capacity was obtained for one and three seconds by recording the vital capacity with the kymograph rotating at 3600 mm. per minute. The maximal breathing capacity was measured by a ratchet-type mechanical integrator. The functional residual capacity was determined by the helium closed-circuit method. Minute ventilation and oxygen consumption were recorded simultaneously, the former with the ratchet-type mechanical integrator and the latter by measuring a straight line of oxygen consumption for at least three minutes. The

*Cardiopulmonary Laboratory, Newark Beth Israel Hospital; supported in part by Public Health Service Grant HF-8685.

ventilation equivalent is defined as the volume of air breathed in liters per 100 ml. of oxygen consumption.

The subjects were required not to smoke for six hours before the studies were performed. The vital capacity, timed vital capacity, maximal breathing capacity, functional residual capacity and ventilation equivalent were then determined with the subject in the sitting position. Each volunteer then smoked two cigarettes of his choosing in approximately 20 minutes inhaling as he normally would, and the identical studies were then immediately repeated.

For 18 of the subjects, an additional procedure was followed. The ventilation equivalent was done not only before and after smoking, but also before and after a waiting period during which the subject did not smoke. The duration of this waiting period was planned approximately to equal the time it took to smoke two cigarettes, about 20 minutes (Table 3).

Results

No significant differences were observed in vital capacity, timed vital capacity, maximal breathing capacity or functional residual capacity

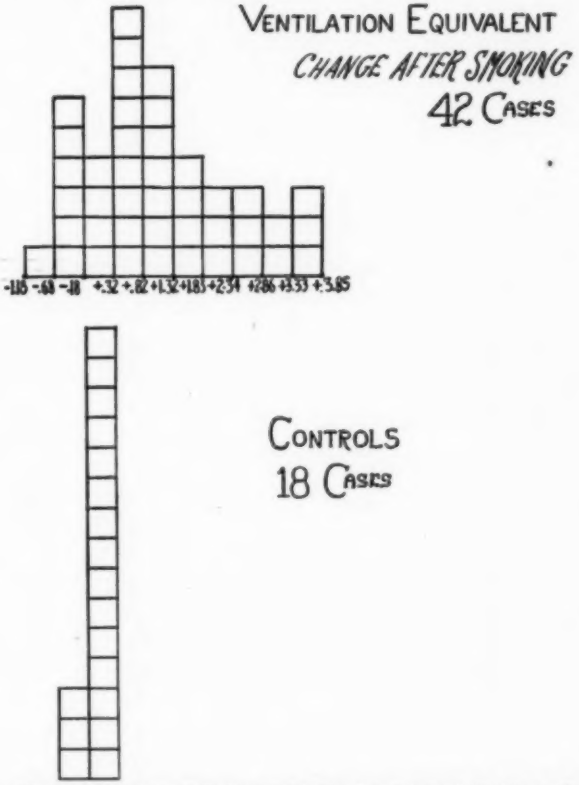

FIGURE 1: The change in ventilation equivalent, expressed in liters of air breathed per 100 mm. of oxygen consumption, after smoking as compared with the change after an equivalent period without smoking ("controls"). Both normals and patients with pulmonary disease are combined in this figure. Each square represents one subject.

TABLE 1—PULMONARY FUNCTION STUDIES BEFORE (B) AND AFTER (A) CIGARETTE SMOKING IN 23 PATIENTS WITH PULMONARY DISEASE

Case No.	Age	Sex	Pulmonary Disease	Degree of Pulmonary Dysfunction	Vital Capacity		Timed Vital Capacity		Maximal Breathing Capacity		Functional Residual Capacity		Minute Ventilation		Oxygen Consump.		Ventil. Equivalent	
					B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	81	M	Bronchiectasis	3	2.40	2.86	56.2 85.0	58.0 86.1	38.4	36.0	4.75	4.52	8.60	10.5	300	200	2.88	5.25
2	53	M	C.D.O.E.	3	1.77	1.55	37.3 64.4	38.8 71.8	24.0	19.2	5.47	5.49	9.70	12.6	270	210	3.61	6.02
3	52	M	Bronchiectasis	1	3.58	3.69	71.0 87.5	73.2 89.5	84.0	102.0	3.22	3.15	12.0	10.8	205	204	5.86	5.29
4	46	M	Tbc—Pleurisy Pleural Effusion	1	3.22	3.34	83.5 100	83.6 100	150.0	138.0	2.81	2.94	10.5	10.0	170	200	6.18	5.00
5	57	M	C.D.O.E.	2	3.00	3.33	30.0 69.0	36.0 67.6	44.4	42.0	5.93	5.13	12.7	13.7	234	260	5.41	5.27
6	65	M	C.D.O.E.	2	4.17	3.64	46.1 69.7	55.3 80.0	48.6	46.8	3.96	3.63	8.40	7.80	233	203	3.61	3.85
7	60	M	C.D.O.E.	3	1.74	1.59	37.9 65.5	41.5 67.9	13.2	12.0	4.79	3.75	7.90	8.90	341	306	2.31	2.92
8	64	M	C.D.O.E.	3	2.54	2.79	47.2 78.0	41.9 68.8	25.2	24.0	6.66	5.47	9.10	9.20	390	300	2.34	3.08
9	67	M	Ca of lung C.D.O.E.	3	2.55	2.61	58.8 78.8	55.4 72.1	36.0	42.0	3.85	3.91	9.90	9.70	300	315	3.30	3.10
10	64	M	Bronchiectasis C.D.O.E.	3	1.41	1.39	37.2 51.7	35.5 50.9	—	—	3.79	4.27	9.00	9.40	300	262	3.00	3.57
11	53	M	C.D.O.E.	2	2.91	2.37	41.2 77.4	39.2 75.1	42.0	48.0	5.35	5.29	6.90	9.55	195	169	3.54	5.67

12	65	M	Bronchiectasis C.D.O.E.	3	1.46	1.20	45.2 80.2	47.5 85.0	18.0	12.4	3.99	4.65	11.11	13.9	360	337	3.08	4.12
13	55	F	Ca of lung	1	3.09	3.20	77.8 100	71.0 100	79.0	72.0	3.42	2.87	5.60	8.50	263	250	2.14	3.40
14	66	M	C.D.O.E.	1	3.48	3.51	73.2 94.8	74.3 95.1	65.0	59.5	3.88	3.43	4.23	3.00	287	145	1.48	2.07
15	67	M	C.D.O.E.	3	2.07	1.95	53.6 82.6	53.8 82.1	60.0	72.4	4.39	4.51	11.7	18.8	190	200	6.16	9.40
16	53	M	C.D.O.E.	3	1.83	1.68	37.7 65.5	32.1 64.3	52.0	60.0	6.54	6.42	16.4	15.9	225	210	7.27	7.58
17	44	M	Fibrocaseous Tbc	3	1.38	1.37	56.5 89.2	63.7 90.0	31.2	27.6	1.80	1.89	7.00	6.00	188	225	3.72	3.54
18	35	M	Fibrocaseous Tbc	3	2.10	1.77	[illegible] 80.1	54.2 88.2	42.0	36.0	3.76	3.82	7.20	10.0	246	190	2.93	5.27
19	53	M	Sarcoidosis	1	2.52	2.61	92.9 97.7	91.0 100	70.4	76.0	3.20	3.07	7.70	9.00	109	105	7.10	8.58
20	48	M	Bronchiectasis C.D.O.E.	1	3.44	3.36	68.2 90.8	75.9 99.2	80.0	84.4	4.24	4.03	5.90	6.00	225	195	2.63	3.08
21	59	F	C.D.O.E.	2	2.25	2.14	71.4 80.0	69.0 73.1	52.0	45.0	3.76	3.82	7.20	10.5	450	400	1.60	2.63
22	74	F	C.D.O.E.	2	1.98	2.04	62.5 73.0	59.0 68.7	38.0	41.2	3.01	3.42	7.50	11.3	420	405	1.79	2.78
23	50	M	Silicosis	2	3.05	3.12	66.7 82.9	59.8 79.9	42.0	44.4	5.29	5.14	5.80	7.13	185	188	3.41	3.81

Pulmonary Disease: C.D.O.E. equals Chronic Diffuse Obstructive Emphysema. *Degree of Pulmonary Dysfunction:* 1 equals Minimal; 2 equals Moderate; 3 equals Severe. *Vital Capacity:* expressed in liters. *Timed Vital Capacity:* expressed in per cent of vital capacity; upper figure represents 1-second timed vital capacity, lower figure represents 3-second timed vital capacity. *Maximal Breathing Capacity:* expressed in liters per minute. *Functional Residual Capacity:* expressed in liters. *Minute Ventilation:* expressed in liters per minute. *Oxygen Consumption:* expressed in millimeters per minute. *Ventilation Equivalent:* expressed as volume of air breathed in liters per 100 millimeters of oxygen consumption.

TABLE 2—PULMONARY FUNCTION STUDIES BEFORE (B) AND AFTER (A) CIGARETTE SMOKING IN 19 NORMAL SUBJECTS (Data as expressed in Table 1)

Case No.	Age	Sex	Vital Capacity		Timed Vital Capacity		Maximal Breathing Capacity		Functional Capacity		Residual Minute Ventilation		Oxygen Consump.		Ventilation Equivalent	
			B	A	B	A	B	A	B	A	B	A	B	A	B	A
24	22	M	4.40	4.61	80.2 97.0	88.7 100	108.0	111.8	2.33	2.46	10.70	13.70	270	240	3.96	5.71
25	23	M	4.38	4.68	76.1 96.5	72.5 97.1	128.5	126.0	2.12	1.82	5.70	8.70	220	150	2.59	5.80
26	25	M	5.07	5.07	81.6 95.8	84.0 97.0	120.5	133.1	2.94	2.81	6.50	8.30	380	360	1.71	2.31
27	21	M	4.95	4.89	80.7 100	81.9 100	138.0	147.0	3.25	3.37	4.88	4.65	225	230	2.17	2.02
28	35	M	5.51	5.54	81.8 97.0	80.2 95.5	114.0	122.5	3.47	3.42	7.80	12.6	206	165	3.79	7.64
29	22	M	4.50	4.41	86.7 97.5	86.5 96.6	153.0	146.6	2.44	3.08	6.15	9.75	165	155	3.73	6.30
30	26	M	4.32	4.36	77.8 93.8	79.2 96.5	162.4	157.0	2.83	2.79	6.0	5.5	370	343	1.62	1.60
31	27	M	4.71	4.89	82.8 100	83.1 100	117.0	110.0	3.11	3.05	3.75	3.75	235	330	1.60	1.15
32	21	M	5.40	5.27	84.4 97.5	85.1 100	162.0	164.5	3.25	2.92	6.25	7.25	275	215	2.27	3.38
33	48	M	4.27	4.12	87.0 100	88.4 100	147.0	142.0	2.41	2.52	7.75	10.5	210	225	3.69	4.67
34	38	F	3.54	3.21	91.0 100	89.0 100	79.5	72.0	1.68	1.76	4.88	8.25	225	200	2.17	4.13
35	30	F	3.25	3.42	75.7 98.5	81.0 97.5	85.0	78.5	2.46	2.62	3.38	9.00	225	175	2.17	5.14
36	49	M	3.95	4.01	83.9 100	81.0 100	97.0	89.5	3.15	2.97	4.88	5.25	210	188	2.32	2.80
37	54	M	3.44	3.51	85.5 97.0	79.0 95.4	90.5	96.0	2.61	2.74	4.18	5.40	240	173	1.72	3.13
38	47	M	3.62	3.57	79.7 98.2	81.0 100	84.0	91.2	3.04	2.97	3.75	5.63	200	165	1.88	3.41
39	41	M	4.35	4.71	80.4 97.0	81.3 100	110.0	114.0	2.34	2.40	4.88	4.50	188	188	2.60	2.40
40	44	M	4.59	4.52	79.8 100	82.0 100	132.0	128.5	2.13	2.09	4.88	6.75	225	113	2.17	6.00
41	36	M	4.20	4.31	83.5 100	80.2 100	148.0	142.5	2.62	2.53	3.40	4.10	165	150	2.06	2.73
42	20	M	3.78	3.83	79.7 100	78.4 100	101.0	108.5	2.31	2.24	4.65	6.20	190	165	2.45	3.76

after cigarette smoking in either patients with pulmonary disease or the normal subjects (Tables 1 and 2).

Striking changes, however, were found in the ventilation equivalent (Figure 1). It was noted that the ventilation equivalent and minute ventilation both increased significantly ($p<.001$) in the normal group after smoking with no significant change in oxygen consumption (Table 2). None of these factors was altered significantly by cigarette smoking in the patients with pulmonary disease, although 18 of the 23 patients in this group showed some increase in ventilation equivalent after smoking (Table 1). No significant change in ventilation equivalent was found in 13 normal subjects and five patients with pulmonary disease after a waiting period in which they did not smoke (Table 3).

Discussion

Our data appear to show quite clearly that in our normal subjects smoking was followed by a significant increase ($p<.001$) in the ventilation equivalent and in minute ventilation (Table 2). Although there was no significant decrease in oxygen consumption, it is likely that the same level of oxygenation was maintained only because of the increased ventilation. Conversely, one may theorize that without the increased ventilation, hypoxia might have resulted.

The mechanism by which smoking interferes with oxygenation of blood is unknown. It has been suggested by Loomis[6] that smoking causes bronchospasm which may interfere with adequate distribution of air. Our studies revealed no evidence of bronchospasm after smoking. Smoking may cause vasospasm[7] and decreased pulmonary capillary blood flow or it may produce a transient alveolo-capillary block. Finally, a combination of these factors may be responsible for impaired oxygenation. The fact remains that the normal individual hyperventilates during and immediately after smoking. It is possible that for some, the pleasurable effects of smoking are actually those sensations which accompany hyperventilation.

The failure of patients with pulmonary disease to increase their ventilation after smoking is more difficult to explain. It is possible that the chronic impairment of transportation of oxygen from the atmosphere to blood induced by the pre-existing pathologic state is so great as compared to the interference caused by smoking that the latter adds little to the total effect and there is no significant change in ventilation. It is a common observation that patients with severe pulmonary dysfunction usually have no subjective increase in respiratory difficulty while smoking.

TABLE 3—MINUTE VENTILATION, OXYGEN CONSUMPTION AND VENTILATION EQUIVALENT BEFORE (B) AND AFTER (A) A WAITING PERIOD OF 20 MINUTES DURING WHICH THE SUBJECTS DID NOT SMOKE (Controls)

Case numbers and data as expressed in Tables 1 and 2

Case No.	Minute Ventilation		Oxygen Consumption		Ventilation Equivalent	
	B	A	B	A	B	A
1	8.25	9.05	270	330	3.06	2.74
2	10.5	10.5	310	290	3.39	3.62
21	6.75	6.90	410	400	1.64	1.72
22	6.60	6.50	360	400	1.83	1.62
23	6.17	5.53	210	180	2.94	3.07
24	12.0	12.5	470	480	2.55	2.60
26	7.10	7.30	330	340	2.15	2.14
30	6.20	6.60	360	390	1.59	1.69
33	8.75	9.00	248	255	3.54	3.53
34	4.72	4.50	235	210	2.01	2.14
35	2.90	3.19	160	180	1.81	1.77
36	4.56	4.38	210	195	2.17	2.24
37	3.67	3.63	220	200	1.67	1.81
38	3.60	3.58	165	200	2.18	1.79
39	4.90	5.20	195	210	2.51	2.47
40	3.86	3.88	170	180	2.27	2.15
41	3.31	3.25	190	180	1.74	1.80
42	4.40	4.55	185	180	2.38	2.52

SUMMARY

Pulmonary function studies consisting of vital capacity, timed vital capacity, maximal breathing capacity, functional residual capacity and ventilation equivalent were performed in a group of 23 patients with various pulmonary disorders and 19 normals before and immediately after smoking two cigarettes. A striking increase in the ventilation equivalent was observed in the normal subjects, probably attributable to impaired oxygenation caused by smoking.

RESUMEN

Los estudios funcionales consistentes en capacidad vital, capacidad vital por segundos, capacidad respiratoria máxima, capacidad funcional residual y equivalente ventilatorio, se hicieron en 23 enfermos con varios padecimientos pulmonares y en 19 sujetos normales anges y después de fumar cigarrillos.

Se observó un notable aumento en el equivalente ventilatorio en los normales, probablemente debido a deficiencia de la oxigenación causada por el fumar.

RESUMÉ

Des études de la fonction pulmonaire consistant dans l'étude de la capacité vitale, de la capacité vitale-minute, de la ventilation maximale, de la capacité résiduelle, et de l'équivalent respiratoire, furent pratiquées dans un groupe de 23 malades atteints de différents désordres pulmonaires et 19 sujets normaux avant et immédiatement après avoid fumé deux cigarettes. Une augmentation frappante du coefficient ventilatoire fut observé che. les sujets normaux, probablement imputable au trouble de l'oxygénation provoqué par la fumée.

ZUSAMMENFASSUNG

Bei 23 Patienten mit verschiedenen Lungenkrankheiten und 19 Gesunden wurden Vitalkapazität, Sekundenkapizität, Atemgrenzwert und funktionelle Residualkapazität sowie das Atemäquivalent vor und unmittelbar nach dem Rauchen von 2 Zigaretten durchgeführt. Bei den Normalen wurde eine auffallende Zunahme des Atemäquivalentes beobachtet, die wahrscheinlich einer gestörten Sauerstoffaufnahme auf Grund des Rauchens zuzuschreiben ist.

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A COMPARISON OF THE *IN VITRO* AND *IN VIVO* ACTIVITY OF ERYTHROMYCIN AND SPIRAMYCIN

In comparative *in vitro* tests, erythromycin was found to be a much more effective antibiotic than spiramycin. When the two antibiotics were combined, their antibiotic activity was enhanced. However, erythromycin exhibit marked differences in their *in vivo* mode of action in mice. Erythromycin appears to have low tissue affinity and is eliminated from the body within 24 hours after its administration. Spiramycin, on the other hand, has marked tissue affinity. It is retained in the organs for more than 24 hours and relatively high concentrations can accumulate during prolonged treatment.

Maniar, A. C., Eidsu, L. and Greenberg, L.: "A Comparison of the *In Vitro* and *In Vivo* Activity of Erythromycin and Spiramycin," *Antiobiot. Chemother.*, 10, 730, 1960.

Tuberculin Sensitivity and Tuberculosis in Nursing and Medical Students

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Introduction

A tuberculosis control program in the University of Maryland Schools of Nursing and Medicine was started in September, 1934 by the physician who was director of the two health services at that time.

The following report represents the experience with these students for the 25 year period from 1934 to 1959, in regard to trend in tuberculin sensitivity and attack rate of clinical tuberculosis while in school. Before the control program was instituted, tuberculosis was diagnosed only after it became sufficiently advanced to produce clinical signs and symptoms. Obviously, the possibilities of contagion were great and many students became infected with tuberculosis. Tuberculin testing and chest x-ray films made early diagnosis and treatment a reality and isolation of active cases lessened the possibility of contagion.

Material and Methods

More than 90 per cent of the students were tuberculin tested and all had chest x-ray films on entrance to school. Re-testing was done on non-reactors at the beginning of each successive year. After 1948, medical students in the junior and senior classes were tested at the beginning and end of the school year, since these were years of maximal exposure to patients. Nursing students have been tested at the beginning and end of each school year. Students who were reactors on admission had chest x-ray films annually, and converters had chest films every three months for a year from the time of conversion, and annually thereafter. Since 1948, all senior students have had chest x-ray films at the end of the school year without regard to their tuberculin status.

Tuberculin records of nursing students were inadequate in 1942 and from 1954 through 1957, but all students had chest x-ray films before graduation.

Old Tuberculin (O.T.) was used for testing until October, 1944. From that time until the present, patch testing (Vollmer) has been used, with doubtful reactions checked with O.T. or purified protein derivative (PPD). In 1959, all freshman and sophomore, and most of the junior and senior medical students were tested with both patch and intermediate strength PPD.

Vaccination of medical students with BCG was considered in 1949, but was not begun. A few students have been vaccinated with this material on their own initiative, but not in sufficient numbers to affect this study. In 1955, BCG was offered to the nursing students, but acceptance and cooperation with follow-up studies were so poor the program was discontinued.

*From the Student Health Service, University of Maryland School of Medicine.

The year used to designate a class refers to the year in which that class entered school.

The three-year nursing curriculum ended in June, 1956. Nursing students now spend two years in college and two years at the University Hospital.

Results of the Study

The total percentage of tuberculin reactors for each class was tabulated for each year in school beginning with the classes entering in September, 1934. Table 1 is an extension of a table of medical student reactors included in a previous publication.[1]

TABLE 1—PERCENTAGE OF TUBERCULIN REACTORS IN UNIVERSITY OF MARYLAND MEDICAL STUDENTS TESTED ANNUALLY, 1955-1959

Entrance Date	First Year		Second Year		Third Year		Fourth Year		End of Fourth Year	
	Number Tested	Per Cent of Reactors	Number Tested	Per Cent of Reactors	Number Tested	Per Cent of Reactors	Number Tested	Per Cent of Reactors	Number Tested	Per Cent of Reactors
Sept. 1955	96	15.6	93	18.2	96	19.8	83	22.9	83	24.1
Sept. 1956	93	11.8	96	15.6	80	18.7	83	33.7		
Sept. 1957	94	10.6	94	12.7	86	12.8				
Sept. 1958	101	13.8	98	16.2						
Sept. 1959	102	11.7*								

This class was tested by patch and intermediate strength PPD.

*Eight additional reactors to Intermediate Strength PPD were found which would make per cent of reactors 17.6.

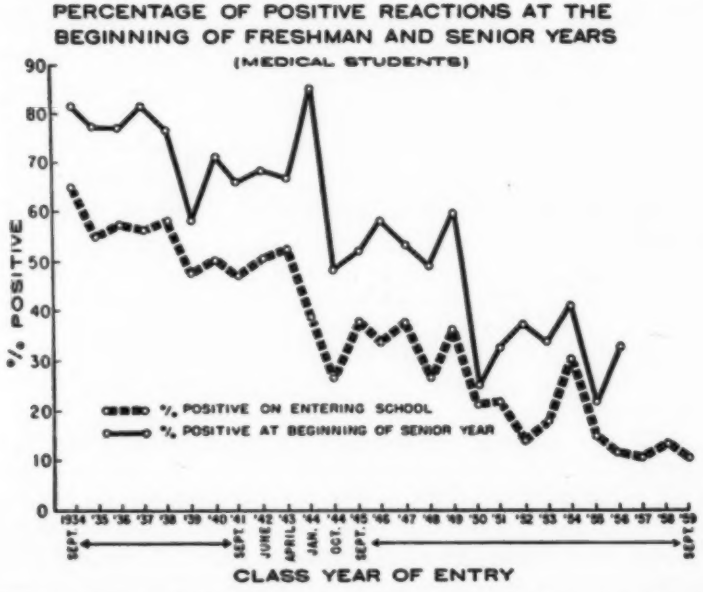

FIGURE 1: Percentage of reactors in medical students at the beginning of freshman and senior years.

The percentage of medical student reactors on matriculation and at the beginning of the fourth year for each class is shown in Figure 1. In 1934, 65.4 per cent of the entering freshmen were reactors, but the percentage has declined steadily. Since 1950, there have been 21 per cent or less reactors, except for the class of September, 1954, which had 30.6 per cent. The class entering in 1959 had 11.7 per cent reactors to patch testing, but intermediate strength PPD done simultaneously revealed eight additional reactors, increasing the percentage to 17.6. Two hundred and two non-reactors in the upper classes, tested by both methods in 1959, yielded three students who reacted to intermediate strength PPD, but not to the patch.

It is suspected that reactions were over-read in the freshman class. This suspicion was strengthened when the sophomore class of 1959 was tested with intermediate strength PPD as a laboratory exercise in Microbiology, and yielded 8.7 per cent reactors as compared to Student Health Service testing with patch and intermediate strength PPD, which yielded 16.2 per cent. All reactors in this group reacted to both tests and, as expected, students in all classes who reacted to the tuberculin patch also reacted to intermediate strength PPD.

The percentage of senior-year reactors shown in Figure 1 is influenced by students who transfer into the upper classes or leave school. This graph does not show the conversion occurring in the senior year because of four classes which had inadequate testing at graduation.

TABLE 2—TUBERCULOSIS INFECTION EXPERIENCE OF MEDICAL STUDENTS, UNIVERSITY OF MARYLAND, 1934-1959

Period Following Admission (Years)	Number of Negative Reactors At Beginning Of Period	Number of Positive Reactors At End Of Period	Per Cent Converted
	1934 - 1939		
0 - 1	216	29	13.4
1 - 2	177	17	9.6
2 - 3	172	34	19.8
3 - 4	136	11	8.0
	1940 - 1944		
0 - 1	289	35	12.1
1 - 2	233	38	16.3
2 - 3	211	45	21.3
3 - 4	92	8	8.7
	1945 - 1949		
0 - 1	275	23	8.3
1 - 2	244	38	15.6
2 - 3	216	27	12.4
3 - 4	189	14	7.4
	1950 - 1954		
0 - 1	375	14	3.7
1 - 2	361	25	6.9
2 - 3	335	24	7.1
3 - 4	202	15	7.4
	1955 - 1959		
0 - 1	315	12	3.8
1 - 2	213	3	1.4
2 - 3	126	10	7.9
3 - 4	64	1	1.5

The true incidence of infection for each year in medical school is shown in Table 2. The non-reactors at matriculation, who had converted when they returned to school for their second year, are tabulated as the reactors for the zero to one-year period. The converters for the second and third year period were tabulated at the beginning of their third and fourth years of school. The seniors who converted were counted at graduation. The classes were grouped in cohorts to provide larger groups for statistical evaluation. For example, in the period 1934-1939, the first year includes all freshman classes during those years.

The first significant decrease in conversion percentages for medical students is shown in the group 1950-1954. These percentages are definitely lower than in any of the preceding groups, ranging from 3.7 per cent for freshmen to 7.4 per cent for seniors, and probably should be even lower, as most of the reactors in the third and fourth years reacted to second strength PPD. The 1955-1959 group shows a similar low rate of conversion. In the 1934-1939 and 1940-1944 groups, the third-year students showed a higher rate of conversion. The 1945-1949 group shows a higher rate for the second year, but the latter groups show little dif-

TABLE 3—PERCENTAGE OF TUBERCULIN REACTORS IN UNIVERSITY OF MARYLAND NURSING STUDENTS TESTED ANNUALLY, 1934-1960

Entrance Date	First Year		Second Year		Third Year		End of Third Year	
	Number Tested	Per Cent of Reactors	Number Tested	Per Cent of Reactors	Number Tested	Per Cent of Reactors	Number Tested	Per Cent of Reactors
Oct. 1934	42	50	28	61	28	79	26	92
Feb. 1935	54	37	34	71	33	85	53	88
Feb. 1936	41	39	21	52	22	68	21	76
Oct. 1937	45	42	31	58	30	83		
Oct. 1938	43	16	29	52	28	61		
Feb. 1939	48	27	34	44				
Oct. 1940	38	37						
Oct. 1941	53	41	46	37	46	63	44	75
Mar. 1942	62	24	51	29	50	36	49	37
Oct. 1943	85	18	55	22	51	35		
Oct. 1944	103	21	85	26	83	31	83	34
Oct. 1945	69	28	59	54	58	59	58	59
Nov. 1946	54	33	46	61	46	65		
Nov. 1947	67	24	43	26	37	32	37	32
Sept. 1948	62	26	53	26	53	32	51	35
Oct. 1949	88	7	68	10	62	11	57	14
Sept. 1950	59	10	49	10	43	16	28	39
Sept. 1951	76	18	47	24				
Sept. 1952	59	3	49	6				
Sept. 1953	39	5						
Sept. 1954								
Sept. 1955								
Sept. 1956								
Sept. 1957								
Sept. 1958	36	11	32	13	32	13		
Sept. 1959	42	5	42	7				

Three-Year Program ended June, 1956. Students now spend two years in college and two years in Nursing School, Baltimore.

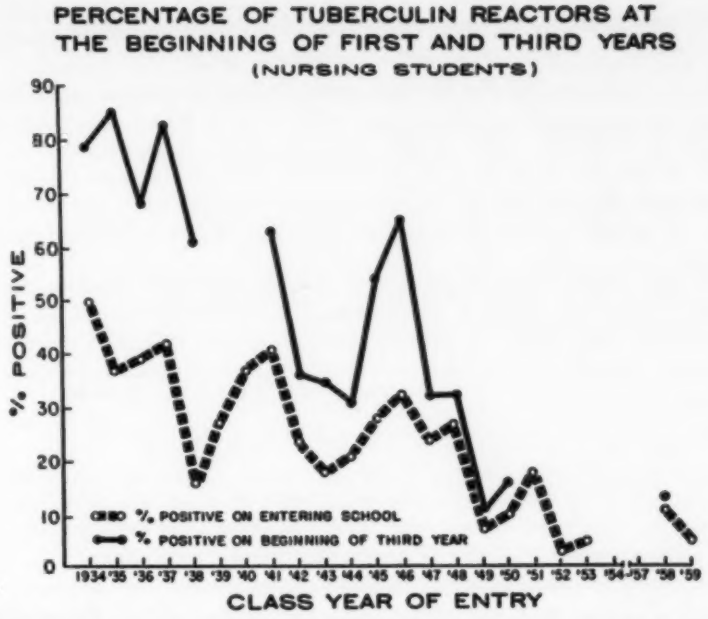

FIGURE 2: Percentage of reactors in nursing students at the beginning of first and third years.

TABLE 4—TUBERCULOUS INFECTION EXPERIENCE OF NURSING STUDENTS, UNIVERSITY OF MARYLAND, 1934-1959

Period Following Admission	Number of Non-reactors at Beginning of Period	Number of Reactors at End of Period	Per Cent Converted
	1934 - 1939		
0 - 1	113	36	31.8
1 - 2	56	22	39.1
2 - 3	16	5	31.2
	1940 - 1944		
0 - 1	184	12	6.5
1 - 2	164	25	15.2
2 - 3	128	8	6.3
	1945 - 1949		
0 - 1	196	26	13.2
1 - 2	165	9	5.5
2 - 3	133	2	1.5
	1950 - 1954		
0 - 1	125	5	4
1 - 2	86	5	5.8
2 - 3	37	5	13.5
Tuberculin Records Inadequate 1954 to 1957			
	1958 - 1959		
0 - 1	68	1	1.5
1 - 2	28	0	

ference in any of the years except for the very low rate of 1.4 per cent for the second year of the most recent group. Conversion in the fourth year has been strikingly similar from 1934 to 1955.

Table 3 and Figure 2 show the percentage of reactors in nursing students for the classes entering from 1934 to 1959. There is a progressive decline from 50 per cent reactors in 1934 to 5 per cent reactors in 1959. These rates are lower than those for the medical students presumably because of the younger age of nursing students. From 1949 to 1959, the reactors have constituted 18 per cent or less of the entering freshman classes.

The percentage of non-reactors who converted each year in nursing school is shown in Table 4. The cohort of 1934-1939 shows a high rate of conversion with all three classes above 31.2 per cent. The cohorts for nursing students after 1940 show much lower, but variable rates of conversion with no academic year showing a consistently higher rate.

Incidence of Clinical Tuberculosis

Medical Students. A total of 17 cases of active tuberculous disease were found in medical students from 1934 to 1959. Of these, 16 were diagnosed from 1934 to January, 1950, the other case occurring in 1953. The student years involved to June, 1950 were 5,521, giving a case rate of 2.89 per 1,000 per annum. The 3,416 student years involved in the last nine years, with only one case of active disease, produce a case rate of 0.29 per 1,000 per annum.

A summary of the cases in medical students has been reported in a previous publication.[1]

Case: The case diagnosed in 1953 will be mentioned briefly because it demonstrates the value of tuberculin conversion as an aid in diagnosis. The student was a non-reactor in September, 1952, his sophomore year. In the summer of 1953, he worked as a psychiatric aide in a Veterans Administration Hospital. Chest x-ray films taken at this hospital in June and September, 1953 were interpreted as normal. On returning to school, his tuberculin reaction was positive and a chest film showed a minimal lesion in his left apex. The previous x-ray films were obtained and the same lesion was found on the September film. Sedimentation rates were normal and gastric washings were negative. He was treated with Distrycin® and sodium PAS for six months, restricted his activity and continued in school. After graduation, the lesion increased in size and it was necessary to re-treat him.

Nursing Students. A survey of the health records of nursing students yielded nine cases of tuberculous disease while in school, the most recent one being diagnosed in December, 1948. The student years involved from September, 1934 to June, 1950, were 2,182, giving a case rate of 4.1 per 1,000 per annum.

A summary of these cases, giving the tuberculin status on entry, date of conversion, date of diagnosis of disease, and clinical features, is given in Table 5.

Case 9 is of special interest because it demonstrates the need of follow-up after graduation. This student entered school in March, 1947 with a positive tuberculin test and normal chest x-ray film. In December, 1948 an x-ray film showed a 2 cm. area of infiltration in the apex of the left lower lobe. Six gastric washings were negative, and sedimentation rates and temperature remained normal. Skin test with first-strength PPD caused a slough. On restricted activity, she continued in school and gained weight. Chest x-ray films showed gradual development of fibrotic change in the lesion. After graduation, she had two normal pregnancies in 1950 and 1951. In December, 1953, she had an episode of left anterior pleural pain, chill, temperature of 101°F., and cough productive of about 150 cc. of sputum daily. She recovered after a few days without treatment. In November, 1954, she was hospitalized because of

TABLE 5—SUMMARY OF CASES OF ACTIVE TUBERCULOSIS

	Name and Sex	Class Year of Entrance	Entrance Tuberculin Test	Date of Conversion	Date Tuberculosis Diagnosed	Case Summary
1	A.B. (F)	1934	Negative		?	Records inadequate: Statement "Had pleurisy July 11, 1935 to September 7, 1935." No Diagnosis. X-ray film October 21, 1936. Normal.
2	M.K. (F)	1936	Positive		October, 1936	*Entrance examination* revealed subcrepitant rales above and below left clavicle anteriorly. X-ray film showed infiltration, left upper lobe and tenting of dome of right diaphragm. Sedimentation rate 26. Advised to leave training for treatment .
3	V.J.C. (F)	1936	Negative	February, 1938	August, 1938	X-ray film April 6, 1938, normal. August 1, 1938, Pleurisy with effusion, left base.
4	E. S. (F)	1937	Negative	October, 1939	October, 1940	Chest x-ray film normal, November 1, 1939. Pleurisy with effusion right, October 29, 1940. Fluid and sputa negative for tubercle bacilli. Admitted to sanatorium December 7, 1940. Discharged to rest four months at home February, 1941. Graduated October, 1941.
5	S.N.L. (F)	1938	Negative	February, 1939	April, 1940	X-ray film April 16, 1940 showed infiltration both upper lobes. Entered Sanatorium and apparently arrested. X-ray film January, 1942 showed miliary spread. Gastric washings yielded tubercle bacilli.
6	M.A.M. (F)	1939			February, 1941	Records lost prior to February 3, 1941. Chest x-ray film at this time showed 2 cm. infiltration behind second rib on left. Sputa negative. Sedimentation rate normal. Sanatorium April 28, 1941 to November 18, 1941. Returned to school February, 1942. X-ray film January, 1942 showed slight fibrosis left apex. Subsequent x-ray films no change. Graduated, 1944.
7	E.P. (F)	1943	Negative	April, 1944	April, 1944	Chest x-ray films November 26, 1943, Normal. April 28, 1944, 1 cm. infiltration behind fifth rib left. May 25, 1944, no change. June 30, 1944, increase in size of infiltration to 2 cm. July 20, 1944, hospitalized University Hospital. X-ray film no change. Sputa and gastrics negative. Sanatorium August 7, 1944 to September 30, 1944. Returned to school January, 1945. X-ray film February 19, 1945, no change in infiltration, presumed fibrotic. Subsequent x-ray films no change.
8	M.E.K. (F)	1945	Negative	May, 1946	November, 1946	Hospitalized November, 1946 with right pleural effusion, T. 99.4. Two thoracenteses yielded 650 cc. and 160 cc. of fluid which was sterile. No tubercle bacilli found on smear or culture. X-ray film after thoracenteses showed only slight blunting of right costophrenic angle. Treated by bed rest three months, with recovery. Subsequent x-ray films normal. Left school for reasons other than health.
9	M.F.S. (F)	1947	Positive		December, 1948	X-ray films normal from May, 1947 through May, 1948. X-ray film December 8, 1948 showed 2 cm. area of infiltration in the apex of the left lower lobe. Six gastric washings and sedimentation rates normal. First strength PPD caused slough. Put on limited duty. Monthly x-ray films showed gradual fibrosis. Gained weight, completed training. After graduation had two normal pregnancies in 1950 and 1951. In December, 1953 had left anterior pleural pain, chill, temperature 101°F. and cough productive of 150 cc. of sputum daily. No treatment. Recovered after a few days. Hospitalized November 1954 because of hemoptysis. X-ray films showed increase in infiltration left lower lobe and stringy infiltration right lower lobe. Bronchogram and bronchoscopy normal. Sputa, gastric washings and bronchial washings negative for tubercle bacilli. Transferred to sanatorium, diagnosis established and disease arrested.

hemoptysis. Chest x-ray films showed an increase in infiltration in the left lower lobe and stringy infiltration in the right lower lobe. The disease was arrested after treatment in a sanatorium.

TABLE 6—ATTACK RATE ACCORDING TO TUBERCULIN STATUS OF CLASSES ENTERING 1934 TO 1950

Status on Entry	Total Number of Students	Number of Cases	Attack Rate
Medical Students			
Positive	747	5	6.69/1,000
Negative	873	11	12.49/1,000
Nursing Students			
Positive	258	1	3.9/1,000
Negative	696	7	10.1/1,000

Attack Rate. The attack rate according to tuberculin status at matriculation is shown in Table 6. As only one case occurred after 1950, the rates are calculated for the period 1934 to 1950. This does not include students who had clinically significant tuberculosis on entering school, being concerned only with the risk of developing disease after entry. Five of 747 medical student reactors developed tuberculosis, an attack rate of 6.69 per 1,000. The 873 non-reactors yielded 11 cases, an attack rate of 12.49 per 1,000. One case developed in 258 nursing student reactors, an attack rate of 3.9 per 1,000. Seven cases occurred in 696 non-reactors, an attack rate of 10.1 per 1,000. One case is not included here because active tuberculosis was found on entrance examination.

In the group of medical students who were non-reactors on entrance, there developed one case of pleurisy with a small apical infiltration, ten cases of minimal disease, and one case of moderately-advanced pulmonary tuberculosis. Three cases of minimal and two of moderately-advanced disease developed in the medical students who were reactors when they entered school. Of the nursing student non-reactors on entrance, four developed pleurisy, one had minimal and one had moderately-advanced pulmonary tuberculosis. In the reactor entrants, the one case which occurred was of minimal disease, recurring six years later in advanced form.

No case of extrapulmonary disease was found except for a medical student who developed a tuberculous chancre on his hand about four months after assisting with autopsies on tuberculous cadavers. A summary of this case is in a previous publication.[1]

Discussion

There has been a striking reduction in the percentage of tuberculin reactors among students entering the University of Maryland Schools of Nursing and Medicine over the 25 years covered by this report. Reactors among entering medical students have decreased from 65.4 per cent in 1934 to 11.7 per cent by patch test and 17.6 per cent by intermediate strength PPD in 1959. The decline in reactors among nursing student entrants has been from 50 per cent in 1934 to 5 per cent in 1959. Mortality rates for the white population of Maryland have shown a decline which is coincident with the decline in the number of reactors in this student population. Palmer and associates[2] found a high correlation between tuberculosis death rates and percentage of tuberculin reactors among Navy recruits. They state that this correlation "must mean that both the frequency of low-dose reactors and the tuberculosis death rates reflect the same general features of tuberculosis in a community." In Maryland, as in other parts of the United States, the morbidity and new case rates have not fallen as rapidly as the mortality rates.

The recent low reactor rates in nursing students is comparable to the rates observed in Navy recruits and college students, in whom Palmer and associates[2] found an average of 8.8 per cent reactors. Drolet and Lowell[3] found similar low percentages ranging from 9 to 11 per cent in Navy and Marine recruits tested from 1949 to 1952. In 1953, there were 5.3 per cent and in 1954, 4.6 per cent reactors in these recruits. The slightly higher percentages in our medical students are presumably due to their average age, being four years older, and to their pre-medical years affording greater opportunity for contact with tuberculosis outside their home environment.

When percentages of reactors at graduation (or at the beginning of their last year if the class was not completely tested at graduation) are considered, the extent of the decreasing danger of infection is realized. Nursing students who matriculated in 1934 had 92 per cent reactors at graduation and medical students who entered the same year had 84 per cent reactors at graduation. The classes graduating in 1959 had 24 per cent medical student reactors and 13 per cent nursing student reactors. It should be noted that this class of nurses spent only two years at the University Hospital, thus reducing their opportunity for infection.

When conversion rates were considered by cohorts to obtain larger groups for better statistical evaluation, it was seen that no academic year has consistently shown a greater risk of conversion than any other. For the nurses, the years 1934 to 1939 showed a high rate of conversion for all three years. Rates from 1940 to 1959 have been much lower and would seem to indicate the beneficial effect of identification and isolation of active cases of tuberculosis in the early years of the control program, as six of the cases occurred in students entering in the years of the first cohort. Student nurses lived in a dormitory, affording greater opportunity for infection. Conversion rates for medical students have been significantly lower since 1950. This may be associated with the fact that only one medical student developed tuberculosis after 1950. The effect of general improvement in therapy of tuberculosis should be noticeable in this period. However, the lower conversion rates in recent years are not adequate reason for complacency, as Szent-Györgyi[4] points out in his survey of reactors in University of Chicago students registered in 1955. This group showed a higher percentage of conversion in medical students than in the general student population. Myers and associates,[5,6] made the same observation for nursing and medical students at the University of Minnesota in 1940.

Case rates in our nursing and medical students to 1950 were high and comparable to the rates calculated for medical students of 62 American schools by Abruzzi and Hummel[7] for the years 1940 to 1950. Their report pointed out the negligible incidence of tuberculosis in these schools after institution of control programs, some including the use of BCG vaccine. The occurrence of only one case in our medical students in the past nine years and no cases in the nursing students for ten years has been without BCG. Nursing and medical students in the control programs reported by Myers, Boynton and Diehl in 1955[8] and 1957[9] also enjoyed an almost zero incidence of disease without BCG vaccination. It is apparent that marked reduction in incidence of tuberculosis can be accomplished by early diagnosis, education, improved treatment, and management of tuberculosis as a contagious disease. Tuberculin testing is a most important factor in the search for tuberculosis and increases in importance as the number of infected individuals diminishes.

The students in the present study exhibited a higher incidence of tuberculous disease among converters. This is similar to the experience of Dickie,[10] Daniels and associates,[11] and others. Conversely, Shipman and Davis[5] found a higher incidence of disease among nurses who were reactors on entrance. Pollack and Cohen,[12] Israel and Long,[14] Myers and associates,[6] and Badger and Ayvazian,[15] found the rates similar in reactors and non-reactors. A study of Navy recruits by Palmer, Jablon and Edwards,[16] showed the risk of developing tuberculosis to be five times greater for the initially-positive than for the non-reactors. When tuberculin conversion rates are low, endogenous reinfection rates in reactors seem high because so few non-reactors are being infected. The number of cases observed in our students has been too small and the period of observation too brief to develop any significant impressions as to severity and course of disease in relation to entrance tuberculin reaction. A post-graduation study should give more reliable information.

SUMMARY

In the 25 year period from 1934 to 1959, 2,497 medical students and 1,223 nursing students have been adequately studied while in school. Tuberculin records of an additional 148 nursing students were lost, but all had adequate x-ray film study.

The percentage of tuberculin reactors at matriculation and graduation has decreased greatly during this period. The lowest percentages of reactors have occurred since 1949 for nursing students, and since 1950 for medical students, indicating less risk of infection in the study of nursing and medicine than in previous years.

Seventeen cases of clinically significant tuberculosis have developed in medical students while in school, 16 of them before June, 1950, and one in 1953.

Nine cases have occurred in nursing students, all prior to 1949.

This recent low morbidity has occurred without the use of BCG vaccination. It is the result of education, early diagnosis and treatment, improved methods of treatment, and management of tuberculosis as a contagious disease.

Tuberculin testing increases in importance as the number of infected individuals decreases.

Nursing and medical students still run a greater risk of tuberculous infection than other student populations and continued vigilance is still necessary.

ACKNOWLEDGMENT: The tuberculosis control programs for the Schools of Nursing and Medicine were brought into being by T. Nelson Carey, M.D., who was Director of both health services in 1934.

The writer gratefully acknowledges the opportunity to study the health records of the nursing students granted by Wilfred H. Townshend, M.D., Director of the Student Nurse Health Service, and Dean Florence M. Gipe, School of Nursing.

RESUMEN

En los 25 años de 1934 a 1959 se han estudiado bien 2,497 estudiantes de medicina y 1,223 estudiantes de enfermería durante su permanencia en la escuela. Se perdieron los registros de tuberculinorreacciones de 148 enfermeras pero en todas hay adecuado estudio radiológico.

El porcentaje de reactores a la tuberculina al matricularse y al graduarse ha decrecido durante ese período. Los porcentajes mas bajos de reactores se observaron desde 1949 para las enfermeras estudiantes y desde 1950 para los estudiantes de medicina lo que indica menor riesgo de infección para ambos grupos que antes.

Diecisiete casos de tuberculosis clínicamente significante se han presentado en estudiantes mientras estaban en la escuela, 16 de ellos antes de junio de 1950 y uno en 1953.

Nueve casos se han observado en estudiantes de enfermería, todos antes de 1949.

Esta reciente baja morbilidad se ha visto sin que se usara BCG.

Es el resultado de la educación, descubrimiento temprano y tratamiento de la tuberculosis como enfermedad contagiosa.

La prueba tuberculínica aumenta en importancia al tiempo que el número de individuos infectados decrece.

Las enfermeras y los estudiantes de medicina aún corren un riesgo ante la infección tuberculosa mayor que otros grupos de población y la vigilancia continua es aún necesaria.

RESUMÉ

Pendant une période de 25 ans allant de 1934 à 1959, 2,497 étudiants en médecine et 1,223 élèves infirmières ont été observés pendant leurs études. Les résultats tuberculiniques de 148 élèves infirmières supplémentaires furent perdus mais toutes avaient été soumises à de bonnest investigations radiologiques.

Le pourcentage des porteurs de réactions positives lors de l'immatriculation et du passage des examens a diminué beaucoup pendant cette période. Les pourcentages les plus faibles de porteurs de réactions positives ont été atteints depuis 1949 chez les élèves infirmières, et depuis 1950 chez les étudiants en médecine, indiquant un risque moindre d'infection dans les études d'infirmière et de médecine que dans les années antérieures.

17 cas de tuberculose cliniquement importante se sont développés chez les étudiants en médecine alors qu'ils étaient en cours d'études, 16 d'entre ces cas avant juin 1950 et un en 1953 .

9 cas sont apparus chez les élèves infirmières, tous avant 1949.

Cette faible morbidité récente est apparue sans l'emploi de vaccination par le B.C.G. C'est le résultat de l'éducation, du diagnostic précoce et du traitement, de l'amélioration des méthodes d etraitement et du comportement vis-à-vis de la tuberculose en la considérant comme une affection contagieuse.

Le test tuberculinique augmente en importance alors que le nombre des individus infectés diminue.

Les élèves infirmières et les étudiants en médecine courent encore un risque plus grand d'infection tuberculeuse que les autres populations scolaires, et une vigilance suivie est encore nécessaire.

ZUSAMMENFASSUNG

Während des 25-jährigen Zeitraums von 1934 bis 1959 wurden 2,497 Medizinstudenten und 1,223 Krankenpflegeschüler während ihres Studiums hinlänglich untersucht. Aufzeichnungen über die Tuberkulinempfindlichkeit von weiteren 148 Krankenpflegeschülern gingen verloten; jedoch hatten sie alle ausreichende röntgenologische Untersuchungen.

Die Verhältniszahl von Tuberkulinreaktoren bei der Erstimmatrikulation und bei der Abschlußprüfung hat während dieser Zeit beträchtlich abgenommen. Die niedrigsten Prozentsätze von Reaktoren ergaben sich ab 1949 für Krankenpflegeschüler und ab 1950 für Medizinstudenten; sie zeigten das geringe Infektionsrisiko bei der Krankenpflege und dem Studium der Medizin im Vergleich zu früheren Jahren. 17 Fälle von klinisch ins gewichtfallender Tuberkulose traten bei Medizinstudenten während ihres Studiums auf, 16 davon vor Juni 1950 und einer im Jahre 1953.

9 Fälle traten unter den Krankenpflegeschülern auf, sämtlich vor 1949.

Diese jetzt so niedrige Morbidität ergab sich ohne Anwendung der BCG-Impfung. Sie ist das Resultat von Erziehung, Frühdiagnose und Behandlung, verbesserter Behadlungsmethoden und Handhabung der Tuberkulose als eine anstreckende Krankheit. Die Prüfung der Tuberkulinempfindlichkeit nimmt an Bedeutung zu in dem Maß, wie sich die Zahl der infizierten Individuen verringert.

Krankenpflegeschüler und Medizinstudenten laufen noch immer eine größere Gefahr, sich mit Tuberkulose zu infizieren, als Studierende anderer Fächer, und eine anhaltende Wachsamkeit ist noch immer erforderlich.

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RAYNAUD'S DISEASE

A case of Raynaud's disease with necropsy is reported in which the clinical picture was dominated by pulmonary hypertension apparently unassociated with any significant pulmonary parenchymal disease. Microscopically cellular intimal proliferation of small pulmonary muscular arteries and arterioles was the most characteristic lesion. In several proximal medium-sized muscular arteries there was necrotizing arteritis with thrombus formation. Similar vascular lesions were not found in other organs, although generalized atherosclerosis and arteriosclerosis were present. The pulmonary vascular changes are thought to represent a local exacerbation of generalized vascular disease, but a specific etiology was not apparent.

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Postoperative Pulmonary Atelectasis*

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The astounding number of surgical operations performed by physicians today has resulted in a greater awareness of atelectasis, a common postoperative pulmonary complication. Although easily recognized and prevented, atelectasis is frequently overlooked, resulting in serious pulmonary impairmment and occasionally surgical mortality.

The word, atelectasis, is derived from the Greek, "atel-ectasis," which denotes incomplete expansion. Although originally used to describe the non-expanded lung observed in stillborn babies,[1] it is now more specifically defined as an airless state of the lung parenchyma resulting from an obstruction of the tributaries serving the lung and a subsequent absorption of the entrapped air by the circulating blood.[2] That this condition occurs following surgery was first observed by Pasteur in 1910.[3] In 1925, Lee and Jackson[4] first demonstrated by bronchoscopy a complete bronchial obstruction by thick, tenacious secretions in a postoperative atelectatic patient.

How frequently postoperative atelectasis occurs has been found to be dependent upon factors such as: pre- and postoperative therapy, type of surgery, and age, sex, and health of the patient. It is more often encountered after upper abdominal or time-consuming operations, in patients who smoke, have respiratory infections, or are aged, and during seasons of increased acute respiratory infections.[5]

According to Dripps and Deming[6] and Thorén[7] there is a higher incidence of atelectasis in men. DeWeese,[8] on the other hand, believes atelectasis to be twice as common in women because of their thoracic rather than abdominal type of respiration.

Because of the use of grossly divergent diagnostic procedures, surgical techniques, and selection of patients by the various investigators, incidence rates ranging from 5 to 47 per cent have been reported in the literature. Thus it may well be sufficient to state that the incidence of postoperative atelectasis is high, and that this clinical condition represents from 90 to 94 per cent of all postoperative pulmonary complications.[7]

The primary cause of atelectasis is at present a controversial subject focused upon three proposed possibilities.

First, it is believed by most of the recent investigators, that atelectasis is primarily the result of broncho-occlusion by secretions of the respiratory tract which are normally evacuated by the cilia, the cough mechanism, and the expulsive force of respiration. If these secretions should accumulate in the respiratory tract and plug a bronchus, aeration of the involved lung segment would be impaired, and the entrapped air would thus cause collapse of the lung.

Second, atelectasis may be the result of reflex nervous stimuli. This is based upon the assumption that the lung and bronchi are neurologically controlled, myoelastic organs which become atelectatic by active broncho-

*Third Prize (tie), 1959 Essay Contest, American College of Chest Physicians.
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spasm or lung contraction. Evidence favoring this etiology is indirect, and includes the work of Bergamini and Shepard[9] and of Santee,[10] who found no demonstrable bronchial occlusion in several cases of massive postoperative atelectasis examined post mortem.

The third possibility is that atelectasis may be due primarily to postoperative hypoventilation. Because respiration is painful and guarded after surgery, it is shallow and rapid and predisposing to fluid accumulation in the small bronchioles. While Beecher[11] gives evidence to support this etiology, Brattström's[1] studies on gross ventilation before and after high laparatomies, show hypoventilation to be insignificant in the production of atelectasis.

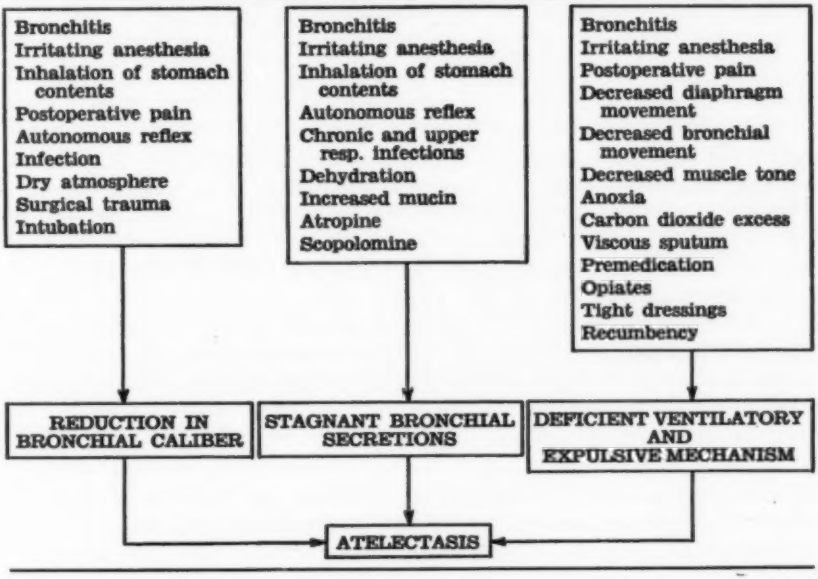
With present experimental evidence, it is not possible to determine which of these etiologies is of paramount importance. More specific etiologic agents to consider are: a decreased ability to expel bronchial secretions due to impairment of the cough reflex by pain or narcotics, a depression of ciliary action by anesthesia, an increased production of secretions after surgery, and a decreased caliber of the bronchial tree resulting from a swollen mucosa, barbiturate, or cyclopropane.[7]

In Table 1 is presented a modification of Brattström's[1] list of presumed etiologic agents of atelectasis.

The diagnosis of atelectasis can be made from a study of the clinical course and symptoms of the postoperative patient. No symptom is evident if only a small area of lung is atelectatic, whereas variable physical findings, changing hourly, may be found in multiple small areas of involvement or patchy atelectasis.[12]

In moderate cases of atelectasis the onset may be sudden or insidious, with subjective symptoms present usually within three days of the oper-

TABLE 1 — ETIOLOGICAL AGENTS OF ATELECTASIS



ation. At first, there may be only tightness in the base of the lung or uncomfortable breathing sensations, but these are soon followed by difficulty with expectoration, chest pains on breathing, coughing and moving, listlessness, and occasionally pleural pain. Elevations of temperature, pulse and respiration during the first, second and third postoperative days should immediately suggest the possibility of atelectasis. The temperature usually rises to 101° F. or higher and the pulse increases disproportionately to 120 or higher. After the first three days the temperature and pulse may decrease, the pulse decreasing more rapidly than the temperature. In the presence of secondary pneumonitis, the temperature remains elevated.[5]

In a massive collapse of the lung, the onset of atelectasis is acute, and the patient appears dangerously ill with mounting fever, sudden, extreme breathlessness or a sensation of suffocation, pleural pain, and profound cyanosis. Unless adequately treated, death can occur within a few hours.[13]

The physical examination of an atelectatic patient presents at first findings of dullness to flatness on percussion, no tactile fremitus or breath and voice sounds, and no rales over a large area. These signs rapidly change to those of solidification, making differentiation from postoperative pneumonia and infarction difficult. Atelectasis is diagnosed when an elevation of the diaphragm and a displacement of the heart and mediastinum to the side of the lesion are detected by physical examination or by the use of x-ray films. A downward inclination of the ribs, a narrowing of the intercostal spaces on the affected side, and a sharply defined segment of non-aerated lung[14] may also be seen on x-ray films.

Because the atelectatic patient is often too ill to be moved and properly positioned, the use of x-ray films is somewhat limited, and the physical signs of percussion and auscultation often cannot be elicited.

In doubtful or serious cases of atelectasis, bronchoscopy may be indicated, not only for diagnostic purposes, but also for treatment, if bronchoocclusion is present.

Recovery from atelectasis is spontaneous in the majority of cases. Although in beginning atelectasis the lung is readily re-expanded, prolonged atelectasis may result in superimposed pulmonary infections, bronchopneumonia, bronchiectasis, and lung abscess. Thus one should be continually aware of atelectasis in the postoperative patient, and clues such as any unexpected fever or delayed convalescence should be investigated promptly.

In early atelectasis, treatment is simple and effective, consisting of procedures to liquefy the mucus plug, release the bronchospasm, and allowing the liquefied plug to slip out either by coughing or by posturing of the patient.

The commonly used therapeutic measures for relief from atelectasis include the following:[5,13]

1) inducing a natural drainage of the lung by frequent changes in posture and by having the patient lie on the side of the unaffected lung.

2) encouraging the patient to cough even though it is painful, by assuring him that the wound is firmly sutured, by giving support to his abdominal incision while coughing, and by restoring the cough reflex by discontinuing the use of narcotics,
3) combating shallow postoperative breathing by having the patient take deep breaths or by the cautious use of carbon dioxide hyperventilation,
4) administering epinephrine to relieve bronchospasm and sulfa drugs or antibiotics to treat pre-existing infections, and
5) aspirating bronchial secretions by bronchoscopy if the occlusion is not decreased within 12 hours after the use of the other procedures.

Recently, newer methods for the treatment of atelectasis have been proposed. Camarata *et al.*[16] use the enzyme, trypsin, or a wetting agent, the detergent, trition A-20, to liquefy the mucus plug; Baker *et al.*[17] administer sodium iodide to the postoperative patient to produce an easy and rapid evacuation of the viscid secretions formed during anesthesia; and Marshall[18] promptly relieves atelectatic symptoms by a compression of the patient's thorax while he is coughing to dislodge any bronchial plugs. Although effective, these methods are not as yet used routinely.

Atelectasis can be prevented if the necessary precautions are taken in the surgical preparation and the postoperative care of a patient. To decrease the incidence of postoperative atelectasis, routine prophylactic procedures, such as those described by Thoré,[7] and Marshall,[18] are practiced in most hospitals today.

Surgery on patients with respiratory tract infections (including even mild colds) are postponed until two weeks after the infection subsides, since infected material may be aspirated during anesthesia and may cause bronchial occlusion. Smoking is decreased to a minimum for a week before the operation. Narcotics are used cautiously because they may produce shallow respiration and suppress the cough reflex. Anesthesia is given at even rates. If spinal anesthesia at higher levels is used, carbon dioxide and oxygen inhalations are administered to insure adequate and complete expansion of the lung, in the event that the accessory respiration muscles become paralyzed.

Postoperatively, the patient is aroused as soon as possible, and his throat and trachea are thoroughly cleaned. A radical change of position hourly is also advocated. For gravity drainage of bronchial secretions and to prevent aspiration of regurgitated gastric contents, the Trendelenburg position may be used during and immediately after surgery. Chemotherapeutics are given prophylactically when necessary.

The use of physiotherapy and hyperventilation procedures have also been proposed for the prevention of atelectasis. Thorén,[7] in a study of 343 cholecystectomy cases, found postoperative pulmonary complications to be minimal when physiotherapy, in the form of respiration and coughing exercises and postural drainage, was used.

The effects of hyperventilation in the prevention of atelectasis were first demonstrated by Scott and Cutler,[19] who had a patient rebreathe into a paper bag to accumulate carbon dioxide and stimulate greater

tidal volumes. Because the face masks used in this method were often leaky and because the subsequently developed, contour masks proved bulky and expensive, Schwartz and Dale[19] proposed the use of a rubber tube to extend the patient's normal respiratory dead space by a liter. By rebreathing in this manner for five minutes every one to two hours postoperatively, significant increases in alveolar pCO_2 and arterial pCO_2 are produced to stimulate the central nervous system, resulting in hyperventilation.

SUMMARY

Atelectasis is still an important postoperative pulmonary complication which threatens the patient who has undergone major surgery. It is generally agreed that the predominant causal factor is a complete bronchial occlusion by secretions, although reflex nervous stimuli have also been implicated to contribute greatly to the occlusion. The role of postoperative hypoventilation in the etiology of atelectasis remains a controversial one.

The diagnosis of atelectasis depends chiefly upon a study of the signs and symptoms, but is aided by the findings of physical examination, x-ray films, and occasionally, bronchoscopy. Treatment and prevention of atelectasis are simple and effective, consisting chiefly of measures to remove the obstruction, such as, coughing, postural drainage, or bronchial catheterization.

RESUMEN

La atelectasia es aún una complicación pulmonar postoperatoria importante que amenaza a los enfermos que han pasado por la cirugía mayor. Se admite generalmente que el factor causal predominante es la oclusión de los bronquios con secreciones, aunque los estímulos de los reflejos nerviosos también pueden estar implicados para contribuir grandemente a la oclusión.

El papel de la hipoventilación postoperatoria en la etiología de la atelectasia es aún discutido.

El diagnóstico de atelectasia depende en especial del estudio de los signos y síntomas pero es auxiliado por los hallazgos del examen físico, las películas de rayos X y ocasionalmente, la broncoscopía. El tratamiento y la prevención de la atelectasia son simples y efectivos consistiendo principalmente en la eliminación de la obstrucción por la tos, canalización postural o cateterización bronquial.

RESUMÉ

L'atélectasie reste encore une complication pulmonaire post-opératoire importante, qui menace le malade qui a subi une sérieuse intervention chirurgicale. Il est admis généralement que le facteur causal prédominant est une occlusion complète des bronches par les sécrétions, bien qu'un réflexe nerveux ait aussi été également considéré comme contribuant fortement à l'occlusion. Le rôle de l'hypoventilation post-opératoire dans l'étiologie de l'atélectasie reste controversé.

Le diagnostic d'atélectasie dépend principalement d'une étude des signes et des symptomes, mais il est aidé par les constatations de l'examen physique, de la radiologie et éventuellement de la bronchoscopie. Le traitement et la prévention de l'atélectasie sont simples et efficaces. Ils consistent principalement à prendre des masures pour éliminer l'obstruction, telles que la provocation de la toux, le drainage de posture et le cathétérisme bronchique.

ZUSAMMENFASSUNG

Die Atelektase bedeutet auch heute noch eine wichtige postoperative pulmonale Komplikation, die die Kranken bedroht, bei denen größere Operationen vorgenommen worden sind. Es besteht allgemeine Übereinstimmung darüber, daß der prödominierende ursächliche Faktor hierfür ein kompletter Bronchialverschluß durch Sekretmassen ist, obwohl reflektorische, nervöse Reize ebenfalls in beträchtlichem Maße am Zustandekommen des Verschlußes beteiligt sind. Die Rolle einer postoperativen Hypoventilation für die Ätiologie der Atelektase bleibt umstritten.

Die Diagnose der Atelektase hängt hauptsächlich von einer Beobachtung der Anzeichen und Symptome ab; sie wird aber erleichtert durch die Befunde der phyikalischen Untersuchung, Röntgenuntersuchung und gelegentlich der Bronchoskopie. Behandlung und Verhütung der Atelektase sind einfach und wirksam; sie bestehen hauptsächlich in Maßnahmen zur Behebung der Obstruktion, sowie Husten, Tieflagerung oder Bronchialkatheterisierung.

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ESOPHAGEAL MONILIASIS

Moniliasis is common in the chronically ill. Severe esophagitis may occur either by extension from the oral cavity or as an isolated infection. The disease may be uncovered early in its course by the striking radiographic findings following a barium swallow. The involved portion of the esophagus shows irritability and spasm. The mucosa has a peculiar granular, cobblestone appearance which may be limited to a segment of the esophagus or extend throughout its length. This appearance is due to a pseudomembranous lining, consisting of *Monilia* and debris. Hypermia, inflammation and edema of the deeper layers are associated with the mucosal ulceration. Detected and treated early, esophageal moniliasis is relatively innocuous and the symptoms are quickly relieved. Undetected, it progresses and may contribute to the patient's death. It is incumbent upon the radiologist to consider monilia infection of the esophagus in debilitated patients with sudden onset of dysphagia and pain on swallowing, since specific and effective treatment is readily available.

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ANTICOAGULANTS IN CORONARY DISEASE

In acute myocardial infarction, the consensus is that all cases should receive anticoagulant therapy. Carefully compiled studies by many independent investigators give statistics which warrant an expected improvement in the mortality rate of from 35 to 50 per cent in such therapy.

In long-term therapy, after a single myocardial infarction our results show the mortality rate to be less than one half that of the controls five years after the attack (44.2 per cent mortality in the control and 18.3 per cent in the treated). These findings generally agree with those in the literature. It is to be noted that especially in the group with recurrent attacks which in the control series has an increased mortality rate, the use of anticoagulant therapy would seem to be even more beneficial.

Ensor, R. E. and Peters, H. R.: "Anticoagulants in Coronary Disease," *Southern Med. J.*, 54: 257, 1961.

Solitary Pulmonary Nodule Due to Ascaris Lumbricoides

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COMMANDER ROBERT M. DIMMETTE, MC, USN
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It has long been established by study of *Ascaris lumbricoides* in man as well as in laboratory hosts, that the larvae, on hatching in the small intestine, migrate through the liver to the lungs. On the eighth to ninth day after infestation, they move farther into the bronchi and then, via the trachea and esophagus, return to the intestine. It has also been shown that the larvae in their migration and development often cause extreme eosinophilia, symptoms such as shortness of breath and cough, and diffuse pulmonary infiltrations which can be roentgenographically recorded. The symptoms resulting from such infestations are transient and it has been believed, from observations in the experimental animal, that any larvae which fail to make the migration from the lungs or other tissues will die within a few weeks and disappear. The similarity of this picture and its possible relationship to eosinophilic lung have long been recognized.[1,2]

The present report is that of a 48-year-old physician who was subjected to thoracotomy for a solitary lesion of the lung suspected of being malignant. This case was selected because to our knowledge it is unique in that it represents an ascaris infestation resulting in a solitary and apparently unchanging nodule of the lung.

D.W.B., a 48-year-old white physician, was admitted to this hospital on January 8, 1959 for evaluation and treatment of a solitary pulmonary nodule which had been discovered at another medical facility. In October, 1957, he had been hospitalized for evaluation of a minor episode of hemoptysis. Chest films, at that time, including posterior-anterior, lateral and lordotic views, were negative except for some prominence of the left hilar shadow which was thought to represent vascular enlargement. Bronchoscopy was negative as were all sputa and bronchial washings. Routine laboratory studies, including white blood cell and differential counts, were within normal limits. He was discharged after one week with a diagnosis of chronic bronchitis. He remained asymptomatic except for "cigarette cough" for over a year when he developed moderate malaise, myalgia and productive cough. A chest roentgenogram revealed a small solitary lesion in the right upper lung field and he was again hospitalized. Sputum culture showed nonhemolytic Streptococcus and *Diplococcus pneumoniae*. Sputum cytology was negative for malignant cells. Purified protein derivative No. 2 was positive. Histoplasmin and coccidioidin skin tests were negative. He was then transferred to us for further evaluation and treatment.

The past medical history and family history were noncontributory. Past personal history revealed that he had smoked 3 to 4 packs of cigarettes daily for 30 years. In 1951, he traveled extensively in Japan and Korea. He has lived for long periods in the southeastern United States and has owned several dogs for some years.

On admission, the temperature was 99.2°F. and the blood pressure 150/80. The general physical examination was essentially negative except for the chest which revealed clear lung fields to percussion, but on auscultation expiratory wheezes were heard over the right anterior upper chest.

Routine laboratory studies were within normal limits. There was no eosinophilia. The sedimentation rate was 14 mm. in one hour. Sputum culture did not reveal bacterial pathogens. Chest x-ray film on February 4, 1959 revealed a 15 mm. noncalcified, fairly well circumscribed soft tissue density at the level of the second right anterior

*National Naval Medical Center. The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

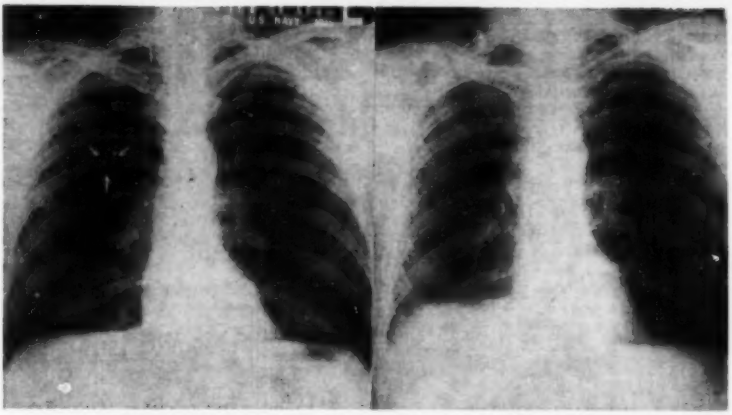

FIGURE 1 FIGURE 2

FIGURE 1: Preoperative film showing lesion in second right anterior interspace.
FIGURE 2: Chest film on 13th postoperative day.

interspace (Fig. 1) which on comparison with films taken on January 21, 1959 showed no interval change. A film of March, 1958 did not show a similar density in this area. Electrocardiogram was normal.

He was given a one week trial on 1,200,000 units of penicillin every 12 hours during which time he remained asymptomatic except for cough. At the end of this time, the pulmonary lesion remained unchanged. Bronchoscopy was negative as were smear and cell blocks on the bronchial washings.

On February 11, 1959, right thoracotomy was performed. The lesion was easily palpated deep in the substance of the lung near the hilus of the upper lobe. Because of its inaccessibility for local excision, right upper lobectomy was deemed advisable and was carried out without incident. There was no significant adenopathy in the hilar area. On sectioning, the lesion was found to be a well circumscribed nodule approximately 2 cm. in diameter. The tissue was grayish-white and friable. On frozen section the pathologist was unable to give any diagnosis other than a reserved opinion that this represented a benign lesion. The peribronchial nodes showed no evidence of disease on frozen section.

Postoperatively he did extremely well and recovery was entirely uneventful (Fig. 2).

On permanent sections, a diagnosis was established of granulomatous lesion, right upper lobe, lung, due to *Ascaris lumbricoides*. The resected specimen consisted of the right upper lobe of the lung which weighed 42 grams. The pleura was thin, smooth, and blue in appearance and showed no alteration in thickness and consistency. The portion of the bronchial tree contained within the lobe was patent with a smooth

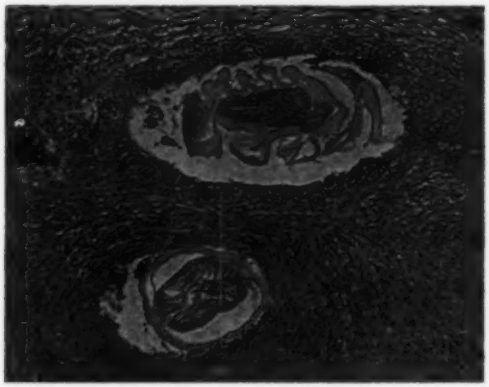

FIGURE 3: Photomicrograph of the nematode segments embedded in dense fibrous connective tissue of the pulmonary granuloma.

lining void of gross pathologic changes. A small amount of mucus was present in the terminal branches of the bronchial tree. The portion of the lung which was removed for frozen section was part of a granuloma adjacent to the hilum. The granuloma and the surrounding reactive lung was 2 cm. in diameter and was composed of friable gray material with central softening.

Microscopically, the granuloma showed central necrosis surrounded by a zone of proliferating fibroblasts which were loosely arranged and numerous chronic inflammatory cells. In the fibroblastic portion of the granuloma, cross sections of a nematode were identified (Fig. 3). The parasite showed partial necrosis. The chitinous portion of the nematode was well preserved. The cross sections of the parasite showed a maximum diameter of 190 microns. The multiple cross sections did not allow a reliable measurement in length. No encysted ova or uterine apparatus could be identified. Although numerous macrophages were present throughout the lung sections, giant or tumor cells were not identified. The remainder of the lung and bronchial tree were within normal limits.

Postoperatively, repeated stool studies were made, all of which were negative. Total eosinophil counts were also done and all were within normal limits.

He was discharged on February 25, 1959.

Discussion

It is interesting to note that in 1957, at the time of this patient's episode of hemoptysis, his eosinophil count was not elevated nor did he at that time exhibit any of the other symptoms of migratory pulmonary larvae. He had since received annual physical examinations and chest x-ray films, but it was not until January, 1959 that the onset of malaise, myalgia and a change in the character of his chronic cough resulted in repeat chest films which revealed this lesion.

It is unlikely that this nodule was in any way related to the initial episode of hemoptysis. The absence of eosinophilia, fever, or hemoptysis at the time the lesion was discovered, and the fact that it was solitary, also suggests that it did not have its origin in the usual cycle of larval migration.

The possibility of the parasite being inhaled and setting up a solitary granulomatous lesion must be considered. The close association that this patient has had over the past years with dogs enhances such likelihood.

This lesion was observed over a period of approximately six weeks and was found to be unchanged for that period. It is impossible to say that it might not have ultimately disappeared had it been considered safe to observe it for a long period of time.

ADDENDUM: The pathological sections containing the parasite were sent to several parasitologists for their impressions. Most agreed that this parasite represented an Ascaris. One observer suggested that possibly this parasite represented Dirofilaria.

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GIANT PULMONARY CYST PRESENTING AS SWELLINGS ON ROOT OF NECK AND UPPER PART OF BACK

The patient, an African woman aged about 60, complained of two swellings on the left side of her neck extending to her back. These were in continuity with another swelling on the left in the upper part of her back. They had appeared three months previously and had grown slowly and were painless. She also gave a history of cough and mucoid sputum.

On examination, the swellings were soft and had the feel of air cushions. There were two large ones in communication with each other. One extended from the left clavicle upwards along the left lateral aspect of the neck and posteriorly to the lower four cervical spinal processes. The other, which was larger, occupied most of the area over the trapezius muscle on the same side, meeting the former swelling at the level of the seventh cervical vertebra. On coughing, they ballooned to double their original size, deflation was slower and was accompanied by a loud hissing sound. The x-ray showed the outline of the air space outside the thorax and what appeared to be a cyst in the upper parts of the right and left lungs. Following repeated aspirations, the swelling disappeared in about five weeks. The patient did not report for follow-up examination.

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ROENTGENOGRAM OF THE MONTH

Edited by Benjamin Felson, M.D.

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San Francisco, California

Clinical Information

A 67 year-old white woman retired school teacher entered the University of California Medical Center with the chief complaint of swelling of the ankles, hips and shoulders. She also reported a 30-pound weight loss and arthritis for 15 years treated with vitamins, calcium tablets and, lately, steroids.

FIGURE 1: Posteroanterior chest film.

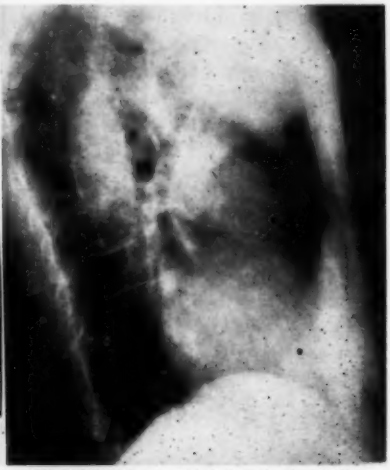

FIGURE 2: Left lateral chest film.

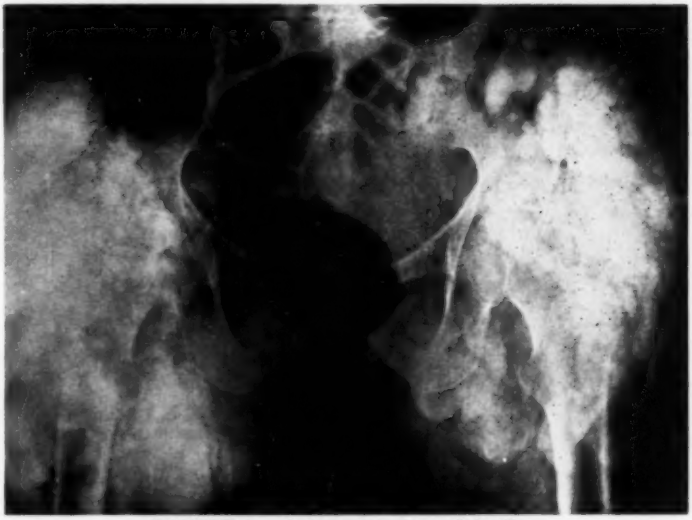

FIGURE 3: Anteroposterior pelvic film.

*Department of Radiology, University of California Medical Center.

Physical examination revealed a wasted elderly white woman with dry skin, numerous nodules on her hands and swelling of her shoulder, hip and ankle joints. In addition, she demonstrated 2+ pitting edema and cardiomegaly. The serum calcium was 6.15 m.Eq./L. and the phosphorus 6.0 mg. per cent. There was albuminuria and the NPN was 185 mg. per cent.

Diagnosis: HYPERVITAMINOSIS D WITH CHRONIC RENAL FAILURE AND CONGESTIVE HEART FAILURE

Further history revealed that she had taken a total of 300,000 i.u. of vitamin D a day each winter for ten years and in the past five years had taken it during the entire year.

Biopsy of a skin nodule showed a calcified giant cell reaction, and aspiration of a shoulder bursa yielded a pasty yellow-white material which contained calcium crystals.

Roentgenograms also demonstrated widespread calcification of a soft nodular type about the shoulders, scapulae, hips, knees, ankles, and hands (Fig. 3). Multiple vessels and the kidneys were also calcified.

Discussion

Since the development of high potency vitamin D preparations and their use in arthritis, many cases of intoxication have been reported. It is interesting to note that only a small number of patients ingesting large amounts of vitamin D, usually as activated ergosterol, develop pathologic changes. Most of them show renal failure, osteoporosis and pathologic calcifications around joints and bursal sacs, and in gouty tophi when these are present. This calcification is quite typical and roentgenographically resembles bunches of grapes.

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The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with brief history. Please submit material to: Benjamin Felson, M.D., chairman, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

DISTRIBUTION OF INH IN ORGANISM OF GUINEA PIGS

Cattaneo and his associates studied the distribution of C_{14} labelled INH in the tuberculous guinea pig. They could demonstrate by detection of radioactivity and chromotographic studies that the INH penetrates normal and caseous lymph nodes.

Cattaneo, C., Spina, G., Ipata, P. L., and Maggini, P.: "La Distribuzione Dell'Isoniazide negli Organi Della Cavia," *Ann. Ist. Carlo Forlanini*, 20:347, 1960.

SECTION ON CARDIOVASCULAR DISEASES

Occluding Thrombi of the Left Atrium

Report of Four Cases Treated Surgically*

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Providence, Rhode Island

Fragmentation of an atrial thrombus with embolization is a serious and frequently disastrous complication of mitral valvuloplasty. Fortunately, the majority of thrombi are well-organized and firmly attached to the atrial wall or to the appendage. If care is taken not to dislodge any adherent clot, satisfactory valvuloplasty ordinarily can be performed by a closed method with a respectably low incidence of operative embolism. In contrast, a free-floating or pedunculated intracavitary thrombus, although less common, poses a formidable problem in surgical management and judgment.

"Ball thrombus" was a name coined by Wood[1] (1814) to describe an organized, unattached clot whose cross sectional diameter was greater than that of the orifice of the chamber containing it. The term has subsequently been used to include pedunculated thrombi also. These thrombi are usually found in the fibrillating left atria of patients with tight mitral stenosis. Their size varies from one cm. in diameter to large masses filling the greater part of the left atrial cavity. Although these thrombi are usually well-organized, they are often partially covered with recent friable clot. Occluding thrombi, whether free-floating or pedunculated, aggravate symptoms of mitral stenosis or cause death by one or any combination of three mechanisms: (1) intermittent occlusion of an already compromised mitral orifice; (2) impaired left atrial filling; or (3) arterial embolism. The lesion would appear to be relatively uncommon. Wallach and his associates[2] found 16 occluding left atrial thrombi among 509 patients with mitral stenosis studied at necropsy, an incidence of 3.1 per cent.

This report is concerned with four cases of occluding left atrial thrombi encountered among 105 operations performed for the relief of mitral stenosis at the Rhode Island Hospital.

Case Reports

Case 1: V. M., 52 year-old man, deaf-mute, was admitted to the Rhode Island Hospital on April 27, 1957 with mild congestive heart failure. There was no history of rheumatic fever or previous arterial emboli. His illness began six years earlier with increasing fatigability and exertional dyspnea. He was treated with digitalis, and subsequently was admitted to another hospital on two occasions because of syncope and chest pain. On each of these admissions, cyanosis of his face, hands and feet was noted.

*From the Department of Surgery, Section of Cardiovascular Surgery, Rhode Island Hospital. Presented at the Spring Meeting of the New England States Chapter, American College of Chest Physicians at Providence, 1960. Supported by a grant from John A. Hartford Foundation, Inc.

Recovery occurred promptly each time. He had had atrial fibrillation for two years. Three months before this admission, a severe episode of congestive heart failure required hospitalization.

On examination, blood pressure was 110/80 mm.Hg. The pulse was 74 and totally irregular. The neck veins were moderately distended. There was edema of the lower extremities. A low-pitched Grade II rumbling diastolic murmur was audible over the apex. The pulmonic second sound was accentuated. The first sound at the apex was distinct. Rales were heard over both lung bases. All peripheral pulses were easily felt. Fluoroscopy showed an enlarged right ventricle; there was no evidence of calcification in the mitral valve region. An electrocardiogram revealed auricular fibrillation with digitalis effect.

The patient responded satisfactorily to a strict medical regimen and he was considered a good candidate for mitral valvuloplasty. An occluding thrombus was not suspected. Eleven days after admission, a thoracotomy was performed through the left fourth intercostal space. The major branches of the aortic arch were encircled with loops of umbilical tape which were used to occlude blood flow during all intracardiac maneuvers. A circumferential purse string of heavy silk was placed around the base of the left atrial appendage. The tip of the appendage was amputated and the atrium was flushed in order to wash out any free thrombi. None was recovered. Whole blood was rapidly infused during this period to compensate for the blood loss. When a finger was introduced into the left atrium, a firm spherical mass, measuring approximately 2.5 cm. in diameter, was felt (Fig. 1). It was attached by a thin pedicle to the posterior atrial wall immediately above the mitral valve orifice. With each ventricular diastole, the mass was felt to enter the depression over a tightly stenosed mitral orifice. During exploration, the thrombus became detached. Several unsuccessful attempts were made to trap the thrombus against the atrial wall with the finger. The mitral valve deliberately had not been opened and the intracardiac finger was withdrawn. During the intra-atrial manipulations, a small tear had occurred in the lateral wall of the atrial appendage proximal to the purse string suture. The appendage was unusual in that it was short and was connected to the atrium by a broad neck. The auricular clamp was then released and the escaping blood, under pressure, effectively delivered the thrombus into the appendage, where it became impacted. Gentle dilatation of the already enlarged opening in the atrial appendage resulted in the thrombus being expelled. The atrium was "flushed-out" again and a satisfactory valvuloplasty was subsequently performed. Examination of the thrombus revealed it to be roughly spherical in shape and firm and rubbery in consistency. Microscopically, it was relatively well-organized except for a peripheral zone of recent clot. The patient made an uncomplicated recovery and was discharged from the hospital on his 16th postoperative day. He has been followed for four years during which time he has had no further episodes of chest pain, syncope or pulmonary edema.

Case 2: A. M., 53 year-old woman, admitted to the Medical Service of the Rhode Island Hospital on April 20, 1958. She complained of pain and numbness of both legs of six hours duration. These symptoms had occurred abruptly, while she was preparing

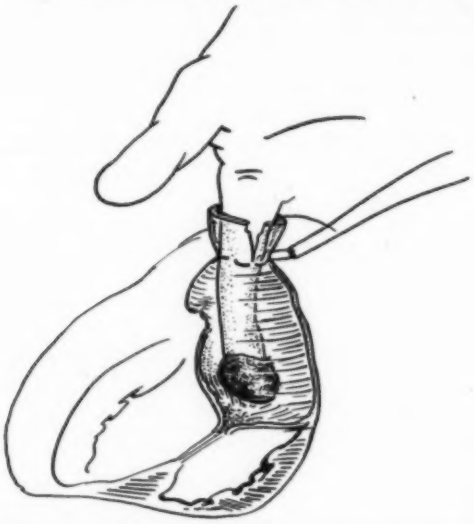

FIGURE 1: Artist's drawing of the occluding thrombus encountered in Case 1.

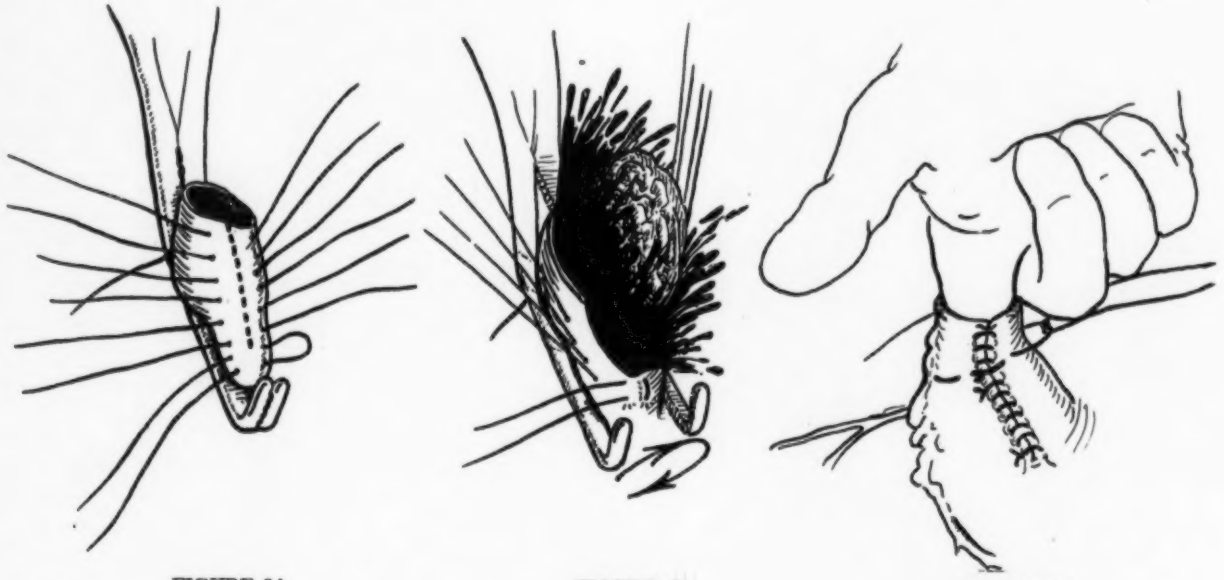

FIGURE 2A FIGURE 2B FIGURE 2C

FIGURE 2: Technique employed to enlarge the atrial opening and "flush-out" the free-floating intracavitary thrombus.

dinner, and had been associated with transient lower abdominal pain and vomiting. She had had rheumatic fever at age 15. Atrial fibrillation together with congestive heart failure had necessitated hospitalization six years before this admission. Digitalis and the intermittent use of diuretics controlled cardiac decompensation, but atrial fibrillation persisted. Four years later she sustained an embolic occlusion of the left brachial artery and a questionable splenic infarction. She did not receive anticoagulant therapy. Subsequently she noted increasing dyspnea and orthopnea.

On examination, the blood pressure was 120/86. The heart rate was 82 and the rhythm grossly irregular. The left lower extremity was cold, mottled and cyanotic. The left femoral pulse was absent. The right leg was cool and slightly mottled. The right femoral pulse was faintly palpable, but the right popliteal pulse was absent. Auscultation of the heart revealed a Grade II apical diastolic murmur and a Grade I systolic murmur along the left sternal border. The pulmonic second sound was accentuated. Except for a moderate elevation of the white-cell count, routine laboratory data were not remarkable. An electrocardiogram confirmed the existence of atrial fibrillation. Fluoroscopy showed an enlarged right ventricle and calcification in the mitral valve region.

Soon after admission, all evidence of ischemia of the right leg disappeared. The appearance of the left lower extremity remained unchanged. Despite a surgical recommendation for prompt embolectomy, the Medical Service elected to anticoagulate the patient and manage the embolism "conservatively." The arterial circulation in the limb improved in the next 24 hours and three days later it was clear that the viability of the left leg had been preserved. After three weeks of careful management with digitalis, mercurials, salt restriction and anticoagulants, the medical attitude became more aggressive and the patient was referred for mitral valvuloplasty. The surgical procedure was undertaken in precisely the same manner as in the case described before, including isolation of the aortic arch branches with umbilical tape. Preliminary flushing of the atrium did not yield any thrombi. Finger exploration of the atrium revealed an unattached irregularly lobulated oval mass which, when later studied, measured 4 x 3 cm. It seemed reasonable to attempt to evacuate the thrombus through an enlarged incision in the atrial wall. A row of opposing mattress sutures was placed in the lateral wall of the atrial appendage and the atrial wall. When traction was applied to these sutures, the appendage and a segment of the lateral atrial wall were elevated and grasped with an atraumatic occluding clamp (Fig. 2A). A 2 cm. incision was made between the opposing sutures beginning at the amputated tip of the appendage. Whole blood was rapidly administered through two venous cannulae. The occluding clamp was released briefly and the thrombus was expelled with the ensuing gush of blood (Fig. 2B). During this maneuver, an assistant maintained continuous traction on stay sutures to ensure that the atrial wall beyond the incision would again be engaged when the occluding clamp was closed. The blood loss, while evacuating the thrombus, was estimated to be between 300 and 400 cc. The incision in the atrium was then carefully closed with a running suture of silk reinforced with interrupted sutures of the same material (Fig. 2C). In spite of calcification of the leaflets, a satisfactory valvuloplasty was accomplished and the patient's recovery was uneventful. In the two years since operation, her cardiac symptoms have improved. However, she has continued to have intermittent claudication in the left lower extremity.

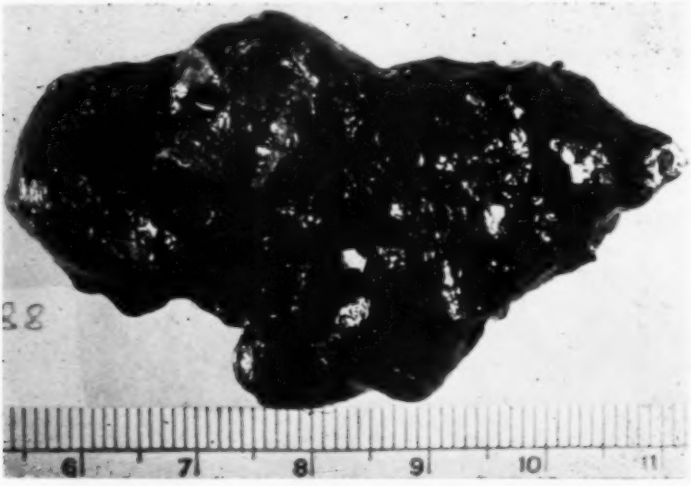

FIGURE 3: Photograph of the atrial thrombus in Case 2.

Examination of the thrombus showed it to be firm and rubbery, composed of two bulbous extremities connected by a narrow waist (Fig. 3). Histologic examination showed it to be organized in many places and mixed with clot of varying age.

Case 3: I. A., 54 year-old woman, was admitted to the Rhode Island Hospital on February 5, 1959 for definitive surgical treatment of mitral stenosis. She had had a heart murmur for 24 years, but could not recall having had rheumatic fever. Three years previously she had developed atrial fibrillation and had been treated with digitalis, diuretics and salt restriction, but nevertheless had frequent attacks of paroxysmal nocturnal dyspnea. Three months before this admission, she had been seen, as an emergency, by the Medical Service because of severe substernal pain and dyspnea. These symptoms disappeared abruptly without specific treatment. She had suffered no previous episodes of embolism.

Examination disclosed a thin, middle-aged woman whose positive physical findings were referrable to her cardiovascular system. Blood pressure was 140/90 mm.Hg. in both arms. A Grade II diastolic, crescendo murmur was heard at the apex. A softer and inconstant systolic murmur was audible to the left of the sternum in the fourth interspace. The pulmonic second sound was accentuated and split. All peripheral pulses were present. The vital capacity of the lung was 2.1 liters. An electrocardiogram showed auricular fibrillation with a ventricular rate of 70. Fluoroscopy revealed a moderately enlarged heart with calcification in the mitral valve region.

On February 23, 1959, an operation similar to the one previously described was performed. A firm, unattached thrombus, measuring 3.5 x 3.5 cm. was found. It was evacuated through a controlled atriotomy with the loss of approximately 400 cc. of blood. This was poorly tolerated and an alarming bradycardia developed. Blood pressure fell to 70/30 mm.Hg. After a period of five minutes, during which whole blood was rapidly infused, cardiac function improved. The mitral valve was tightly stenosed and valvuloplasty was performed with difficulty. Satisfactory incision of both commissures was accomplished, but extensive calcification precluded good mobilization of the valve cusps. Retained bronchial secretions with atelectasis complicated an otherwise satisfactory postoperative course. The patient was discharged from the hospital two weeks following operation. Seventeen months have elapsed since operation and the patient has had no episodes of paroxysmal nocturnal dyspnea. No late embolism has occurred.

Examination of thrombus showed it to be roughly conical in shape. An indented ridge at the tip conformed to the size of the stenosed valve orifice (Fig. 4). The histologic picture was varied. The base of the thrombus was well-organized and covered with endothelium. Peripherally, there was a mixture of clot of varying age showing stratification.

Case 4: L. M., 53 year-old woman, admitted December 6, 1959 with intractable cardiac failure. She was known to have had mitral stenosis for 43 years. She had had

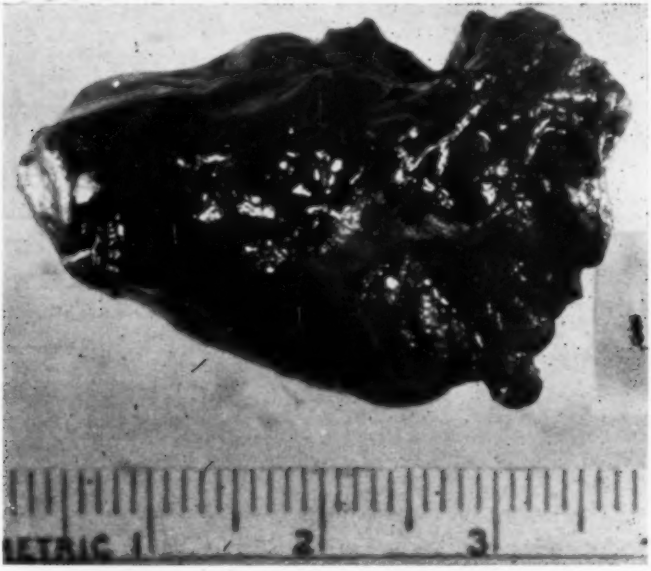

FIGURE 4: The thrombus recovered from Case 3.

three uncomplicated pregnancies and had been relatively free of symptoms until one and one-half years before admission. At that time, dyspnea, cough and peripheral edema responded to treatment with digitalis, mercurials and salt restriction. Three months before admission, an effort to anesthetize her for the removal of several carious teeth was frustrated by the development of severe cardiac arrhythmias. Later she developed atrial fibrillation, a dry, nonproductive cough, and recurrent edema refractory to full doses of digitalis and diuretics. In spite of increasing dyspnea, it was of interest that the patient obtained maximum relief in her breathing by lying prone in bed. All other positions, except sitting upright, resulted in severe dyspnea and paroxysms of coughing.

Examination disclosed a small, thin, chronically ill woman lying on her abdomen in bed. Her nose, fingers and toes were cyanotic. Her neck veins were distended. There were rales at both lung bases. The heart was enlarged to the left. Blood pressure was 115/80 and the heart rate was 100 and totally irregular. A loud, high-pitched, squeaking murmur was heard along the left sternal border. A softer diastolic murmur was heard over the apex. The second sound in the pulmonary area was accentuated. The liver was felt five finger-breadths below the costal margin. There was pitting edema of the sacrum and the lower extremities. An electrocardiogram showed fibrillation with right ventricular hypertrophy. Fluoroscopy disclosed an enlarged heart with a prominent pulmonary conus, evidence of calcification in the region of the mitral valve, and bilateral pleural effusions.

Her symptoms became worse in spite of intensive medical treatment, and it was the consensus that her prognosis was hopeless without surgical treatment. Open operation was elected, since her mitral valve was known to be extensively calcified and the clinical findings suggested the presence of an occluding intra-atrial thrombus. In preparation for the definitive cardiac operation, tracheotomy was performed with the patient in the sitting position. On December 19, 1959, right thoracotomy through the bed of the resected fifth rib was performed. The superior vena cava was cannulated through the right atrial appendage and the inferior vena cava from below, through an incision in the right common femoral vein. Arterial return was through a stainless steel cannula introduced into the right femoral artery. Total heart-lung by-pass was carried out for one hour and 56 minutes, using a heart-lung machine which we have previously described.[3] The left atrium was opened widely posterior to the interatrial sulcus. A pedunculated thrombus, measuring 3 x 3 x 4 cm. was found attached to a thrombus filling the left atrial appendage (Fig. 5). The mitral valve was extensively calcified and tightly stenosed. A gauze sponge was packed into the stenosed valve orifice to trap any thrombotic fragments and the friable thrombus was evacuated in several pieces. The orifice of the atrial appendage was then closed from within the atrium with a running suture of silk. A mitral commissurotomy was achieved under direct vision with the use of appropriate instruments. Although both the anterior and posterior commissures were adequately incised to the valve annulus, dense calcification in the region of the posterior commissure rendered the valve leaflets immobile. An

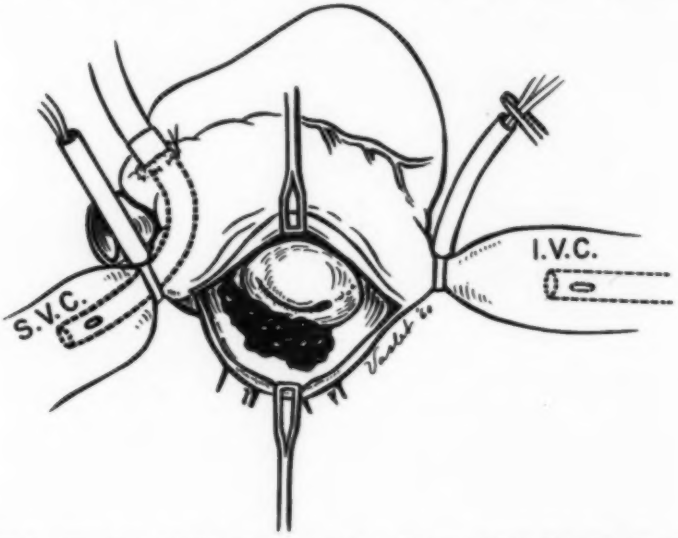

FIGURE 5: Drawing showing the thrombus as it appeared to the surgeon at open-operation.

edematous atrial wall was closed with difficulty. After the circulation had been re-established, it was necessary to return to partial cardiopulmonary by-pass several times in order to finally achieve a blood-tight closure of the atrium. She tolerated the procedure well and was awake, responding to questions, as the last skin sutures were being placed. Her postoperative course was gratifying in the first 24 hours. She was alert and cooperative. The serum electrolytes and pH showed no deviation from normal. Venous pressure varied from 10 to 15 mm.Hg. and systolic arterial blood pressure remained at 100 mm.Hg. Early on her second postoperative day, however, she developed digital cyanosis with a progressive fall in blood pressure despite an adequate blood volume and normal blood chemistry. Death occurred abruptly 48 hours following operation. Necropsy revealed no obvious anatomic cause of death. All suture lines were intact. The heart was enlarged, pale and flabby. Microscopically, the left ventricular myocardium was infiltrated with fat. The cause of death was considered to be due to chronic left ventricular insufficiency.

Discussion

An accurate clinical diagnosis of an occluding intra-atrial thrombus complicating tight mitral stenosis is rarely made ante-mortem.[4] The clinical picture is usually one of severe mitral stenosis. Several clinical clues including peripheral cyanosis, episodes of syncope, frequent attacks of paroxysmal dyspnea, ischemic chest pain, changing murmurs and relief of dyspnea in the knee-chest or prone positions have been described. In retrospect the signs and symptoms in the first three patients described above suggested, but were not diagnostic of intermittent ball-valve occlusion of the mitral valve. The clinical course, peripheral cyanosis and the postural relief of dyspnea encountered in Case 4 resulted in an accurate clinical diagnosis being made. Angiocardiography as described by Steinberg[5] will demonstrate intra-atrial thrombi and is perhaps the most suitable method of making a correct pre-operative diagnosis. Routine use of angiocardiography, however, in the pre-operative evaluation of the severely ill patient with tight mitral stenosis, chronic atrial fibrillation and/or a history of previous embolism, is debatable.

The methods employed in removing intracavitary thrombi, encountered unexpectedly during mitral valvuloplasty, depend, to a great extent, upon the size and age of the thrombus. Clearly, a large ball thrombus requires an open technique, using hypothermia or a pump-oxygenator for its safe removal. On the other hand, small (2 cm. in diameter or under) thrombi can usually be "flushed-out" through the conventional opening in the atrial appendage. Firm thrombi of intermediate size, however, constitute a problem. Class IV patients with tight mitral stenosis tolerate operation poorly unless a reasonably satisfactory opening in the mitral valve is achieved. Thus, when an occluding thrombus is found unexpectedly during the closed operation for mitral stenosis, it would appear reasonable to attempt to "flush out" the thrombus and proceed with an effective mitral commissurotomy. It is of interest that among 29 ball thrombi collected by Radding,[6] 20 ranged from 2.5 to 3.5 cm. in diameter. This would indicate that a significant number of intracavitary thrombi might be removed by methods less elaborate than caval occlusion or cardiopulmonary by-pass. For extracting soft intracavitary clot, Julian[7] advocated the use of strong suction through a glass tube. He did not recommend this method, however, where an organized thrombus might occlude the aspirator and become fragmented. Jamison and his associates[8] described a method whereby the thrombus was grasped with a Kelly clamp and withdrawn through the atrial appendage. They did not mention how often fragmentation occurred. Some authors[2,3] have described performing a mitral valvuloplasty before dealing with the intracavitary thrombus. This practice would appear to be unwise because the thrombus might escape into the ventricle where it could fatally occlude the outflow tract, or embolize to the aortic bifurcation. The technique employed in the first three patients described above was chosen to minimize the hazard of fragmenting the thrombus. Its effectiveness depended upon the presence of a tight mitral valve which confined the thrombus to the atrium and resulted in an elevated atrial pressure sufficient to eject the thrombus during the brief period the atriotomy was open. Bailey[10] and others[11] have shown that a short incision in the atrial wall may be made with reasonable safety if it is controlled with appropriately placed stay or mattress sutures. A short incision (never longer than 2 cm.) extending from the waist of the appendage into the atrial wall enlarged the atrial opening enough to permit passage of the thrombus in two of the patients described. The size of the thrombus and the configuration of the atrial appendage in the first patient simplified the technical problem and blood loss was minimal. In the third patient, a larger atrial opening resulted in significant blood loss. This patient tolerated hemorrhage poorly and her condition was precarious for several minutes after the thrombus had been removed. Rapid transfusion of blood through two large venous portals, however, quickly restored the circulating blood volume. Admittedly, sudden alterations in blood volume are not well tolerated by patients with severe mitral stenosis. However, in evaluating the overall risk, the undesirable effects of transient hypovolemia are, at least, subject to prompt treatment. On the other hand, a shower of emboli from a fragmented thrombus is a disaster in which the surgeon finds himself helpless. In the fourth patient, where the presence of an occluding intra-atrial thrombus was anticipated, an open method

utilizing cardiopulmonary by-pass was elected. The technical facility in dealing with the intracavitary thrombus under direct vision convinced us of the superiority of this method, and we would employ an open technique again when an occluding thrombus was suspected. Merendino[12] has recently pointed out that the mortality for Class IV patients undergoing direct vision commissurotomy is rapidly approaching that of the closed method. It would appear that the day is near when all patients suspected of having any intra-atrial clot, *e.g.*, patients having atrial fibrillation with or without a history of previous embolization, may be more effectively treated with an open operation.

SUMMARY

Among the morphologic variants of left atrial thrombi, the unattached ball or pedunculated thrombus poses the greatest problem in surgical management and judgment. Clearly, large occluding thrombi require an open technique for their safe removal. On the other hand, a number of intermediate-sized thrombi can be treated surgically by less elaborate means when encountered unexpectedly. Four clinical cases encountered among 105 operations for the relief of mitral stenosis at the Rhode Island Hospital are presented to illustrate the problem in diagnosis and surgical management. The surgical technique employed in three patients in whom free-floating intra-atrial thrombi were encountered unexpectedly was chosen in an effort to avoid fragmenting the thrombus. It took advantage of a tight mitral stenosis which effectively restricted the thrombus to the atrium and created an elevated atrial pressure sufficient to expel the thrombus through an enlarged but suture-controlled atriotomy. A fourth patient was suspected of having an occluding thrombus and underwent an open operation.

RESUMEN

Entre las variantes morfologicas de la trombosis atrial izquierda, el trombo esférico o pedunculado presenta el problema mayor en el tratamiento quirurgico y en la decision.

Claramente, los trombos grandes oclusivos requieren una técnica abierta para su extracción segura. Por otra parte, cierto número de trombos de tamaño intermedio, pueden ser tratados quirurgicamente por procedimientos menos complicados cuando se encuentran inesperadamente. Cuatro casos ciínicos encontrados entre 105 operaciones por estenosis mitral en el Hospital Rhode Island se presentan para ilustrar el problema del diagnóstico y del tratamiento. La técnica quirúrgica empleada en tres enfermos en quienes había trombos libremente chocando dentro de la cavidad atrial se escogió para evitar la fragmentación del trombo. Se aprovechó la ventaja de que había una estehosis marcada que restringia la posición del trombo a la aurícula y creaba una presión suficiente para expulsar el trombo a través de una atriotomía grande pero controlable por la sutura. Un cuarto enfermo fue sospechoso de tener un trombo oclusivo y se trató por operación a cielo abierto.

RESUMÉ

Parmi les variétés morphologiques de thrombus auriculaires gauches, le thrombus libre en forme de balle et le thrombus pédiculé posent le plus grand problème dans la conduite chirurgicale et l'appréciation. Clairement, des thrombus volumineux faisant obstruction demandent une technique à coeur ouvert pour que leur exérèse puisse être réalisée sans danger. D'un autre côté, un nombre de thrombus de taille intermédiaire peuvent être traités chirurgicalement par des procédés plus simples quand on les rencontre d'une façon inattendue. Quatre cas cliniques rencontrés sur 105 opérations de sténose mitrale à l'Hôpital de Rhode Island sont présentés pour illustrer le problème du diagnostic et de la conduite chirurgicale. La technique chirurgicale utilisée pour trois malades chez lesquels on rencontra d'une façon inattendue des thrombus intra-auriculaires flottant librement fut choisie de façon à éviter la fragmentation du thrombus. Elle tira parti d'une étroite sténose mitrale qui limita effectivement le thrombus à l'oreillette et créa une élévation de la pression artérielle suffisante pour expulser le thrombus à travers une atriotomie élargie mais contrôlée par la suture. Un quatrième malade fut soupçonné d'avoir un thrombus occlusif, et fut soumis à une opération à coeur ouvert.

ZUSAMMENFASSUNG

Unter den morphologischen Varianten der Thromben des linken Vorhofes stellt die undefestigte Kugel oder der gestielte Thrombus bei der chirurgischen Behandlung und Beurteilung des größte Problem. Das einwandfreie, große, verschliessende Thromben erfordern eine offene Technik zu ihrer sicheren Beseitigung. Auf der anderen Seite kann eine Zahl von Thromben von intermediärer Größe chirurgisch von mittels weniger eingriefender Methoden angegangen werden, wenn man unerwarteter Weise auf sie stößt. Bericht über 4 klinische Fälle aus dem Rhode-Island-Krankenhaus zur Veranschaulichung des Problems der Diagnose und chirurgischen Behandlung; sie fanden sich unter 105 Operationen zur Behebung einer Mitralstenose. Das bei drei Kranken, bei denen freischwimmende intraatrielle Thromben unerwarteter Weise angetroffen wurden, zur Anwendung gebrachte chirurgische Vorgehen wurde gewält

in dem Bemühen, eine Fragmentierung des Thrombus zu vermeiden. Es zog Nutzen von einer engen Mitralstenose, die den Thrombus tatsächlich auf den Vorhof beschränkte und zu einer Erhöhung des Vorhofdruckes führte, der ausreichte, den Thrombus durch eine erweiterte, aber mittels Naht unter Kontrolle gehaltene Atriotomie herauszudrücken. Bei einem vierten Patienten bestand die Vermutung, daß ein verschliessender Thrombus vorläge, und er wurde daher mit der offenen Methode behandelt.

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PULMONARY EMPHYSEMA: ETIOLOGIC FACTORS AND CLINICAL FORMS

Chronic pulmonary emphysema is considered in terms of the major etiologic forces producing this disease. Three basic forms are described: a) chronic bronchitis and emphysema, b) pulmonary fibrosis and emphysema, and c) nonobstructive bullous emphysema.

Within the category of chronic bronchitis and emphysema, two chief clinical forms can be distinguished: a) obstructive emphysema with ventilatory insufficiency, and b) obstructive emphysema with ventilatory insufficiency and alveolar hypoventilation.

In the emphysema associated with pulmonary fibrosis, the basic etiologic forces are: a) traction, and b) obstruction.

The class of primarily nonobstructive bullous emphysema is presented as a disease in which the etiologic factor is an essential destruction or "atrophy" of respiratory tissues. Secondary air passage obstruction, however, occurs from various mechanical causes, and is an important and almost inevitable complication of this disease.

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The Differential Diagnosis of Pulmonary Arteriovenous Fistula*

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The clinical diagnosis of pulmonary arteriovenous fistula has been made with increasing frequency during the past ten years.[1-3] In its most typical form, this disease entity is now easily recognized and often cured with appropriate surgical management. In this paper, variations in the clinical manifestations are discussed, and the importance of a high index of suspicion in evaluating both abnormal chest roentgenograms and single signs or symptoms is emphasized. Nine case reports are presented and the differential diagnosis is reviewed.

On the chest roentgenogram, these lesions characteristically present as peripheral round opacities connected to the hilum by two band-like densities representing the afferent and efferent vessels.[4] Fluoroscopic examination typically shows pulsation of the mass, a decrease in size with the Valsalva test and an increase in size following the Mueller maneuver. The latter changes are frequently subtle, however, and may not be observed.[1,4]

The x-ray film appearance is most frequently confused with tuberculoma or carcinoma. Indeed, some patients have received sanatorium care because of the erroneous diagnosis of tuberculosis.[5] Planigraphy may aid in the differential diagnosis by demonstrating the presence or absence of calcification, cavitation, or communicating hilar vessels.

Though not included in the earliest descriptions of this disease, pulmonary arteriovenous fistulae are commonly a manifestation of hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease). In a patient with an abnormal chest x-ray film, the presence of skin or mucous membrane telangiectases or a history of epistaxis, melena or hemoptysis in either the patient or a blood relative suggests the possibility of pulmonary arteriovenous fistula.[1,6-8]

The classical triad of signs and symptoms associated with pulmonary arteriovenous fistula includes clubbing of the fingers, cyanosis, and polycythemia.[9] These findings result directly from the basic pathophysiologic defect, *i.e.*, a right-to-left shunt with secondary arterial oxygen unsaturation. Their absence, however, does not rule out a fistula, for the amount of venous blood shunted to the pulmonary vein may not be sufficient to produce significant hypoxemia.[10] In addition, bleeding episodes may signalize the development of polycythemia.[11]

In the presence of digital clubbing, cyanosis and polycythemia, it is understandable that an erroneous diagnosis of congenital heart disease or polycythemia vera may be made.[6,12-15] Frequently, adding to the confusion is the presence of a murmur which may be transmitted to the heart. However, the extracardiac location of the bruit and its usual increase in intensity during inspiration are evidence against a congenital

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cardiac lesion. In addition, cardiac catheterization may be helpful when it demonstrates a right-to-left shunt without other apparent anatomic abnormality. Finally, the presence of a normal-sized spleen, normal white blood cell and platelet counts, and peripheral arterial oxygen unsaturation make the diagnosis of polycythemia vera unlikely.

The presence of accompanying central nervous system signs may cause additional diagnostic confusion. Many of these patients complain of paresthesias, headaches, vertigo or syncope and some have had cerebral vascular accidents and brain abscesses. The explanation of these phenomena remains obscure. Whether they result directly from hypoxemia, from the secondary polycythemia, or the shunting of air or septic material from the venous circulation directly to the brain is not yet established.[5,10,16-18]

Once the possibility of pulmonary arteriovenous fistula has been considered, a definitive diagnosis can usually be made by angiocardiography. The importance of this procedure in confirming the diagnosis is universally accepted. Equally important is the demonstration of multiple fistulae frequently present in one or both lungs.[19]

If the physiologic defect is severe enough, surgical resection of the lesion(s) is indicated.[2,3] Single and multiple stage procedures on one or both lungs have been described.[5] Some authorities advocate surgical therapy for all patients so afflicted, even when asymptomatic.[2] This is predicated upon the high incidence of potentially serious complications, particularly hemorrhage and brain abscesses. It is of interest that heart failure and cardiac enlargement are not among the usual sequelae of pulmonary vascular fistulae, presumably because of the low pressures in the pulmonary circuit.

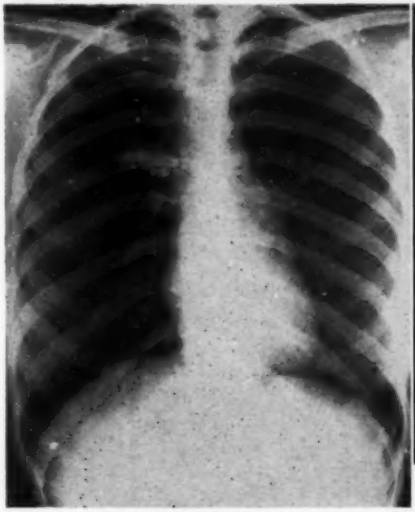

FIGURE 1A

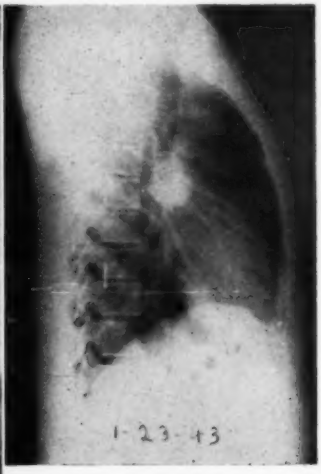

FIGURE 1B

FIGURE 1 (Case 1): (A) A round dense mass is seen in the right hilar region. (B) A lateral view of the angiogram demonstrates the vascular nature of the lesion.

Case Presentations

The following case reports include both typical and atypical features of pulmonary arteriovenous fistulae along with differential diagnostic considerations.

Case 1: (Fig. 1) This 22 year-old woman complained of repeated epistaxis over a two-year period. However, there was no history of cyanosis, convulsive disorders, or other significant complaints.

Pertinent physical findings included the presence of telangiectases on the lower lip. A systolic bruit was heard over the right second and third anterior interspaces, but there was no diastolic component. The heart size was normal. The blood pressure was 110/70.

The chest films revealed a dense rounded mass in the right hilar region. Angiography confirmed the vascular nature of the lesion. Electrocardiographic tracings were normal. The erythrocyte count was 6.7 million/mm.^{3} and the hemoglobin was 18.5 Gm. per cent.

Comment: The diagnosis of pulmonary arteriovenous fistula was made on the basis of the typical roentgenographic findings and the clinical history. Angiography confirmed the diagnosis.

Case 2: (Fig. 2) This 28 year-old white man had a pneumonic lesion four years previously while on Army duty in the region of San Antonio, Texas. The symptoms improved rapidly, but a residual pulmonary infiltrate persisted. The coccidioidin skin test was positive; the tuberculin test was negative. Cyanosis, clubbing, and central nervous system symptoms were absent.

Comments: The granulomatous nature of the lesion was suspected by the x-ray film appearance and the positive coccidioidin skin test. Since carcinoma could not be ruled out, thoracotomy was advised. Surgical exploration and biopsy confirmed the diagnosis of coccidioidomycosis.

Case 3: (Fig. 3) This 24 year-old man gave a six-year history of cyanosis and digital clubbing. He had occasional episodes of hemoptysis and epistaxis. There was a soft systolic murmur over the left mid-lung field posteriorly and the pulmonic area anteriorly.

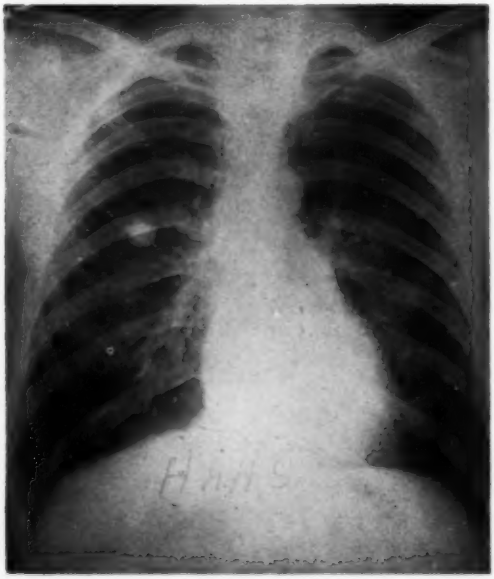

FIGURE 2 (Case 2): A right parahilar mass with hilar bronchovascular prominence is shown. In the PA film, the appearance is similar to Figure 1A. Note the absence of vessels leading directly to the mass. On thoracotomy this lesion was shown to be a granuloma of coccidioidomycosis.

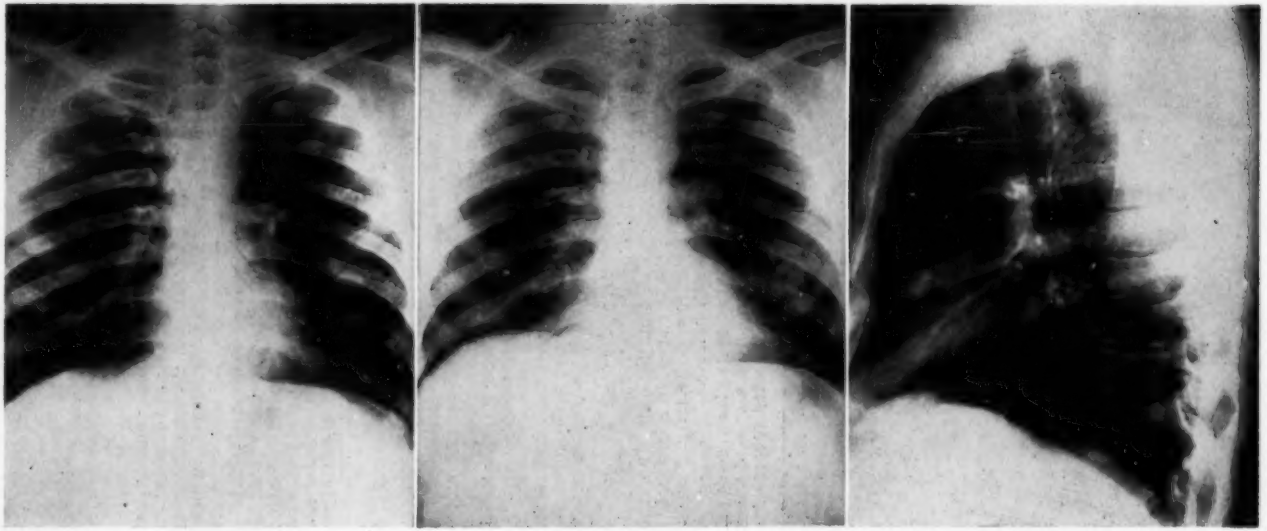

FIGURE 3A FIGURE 3B FIGURE 3C

FIGURE 3 (Case 3): (A) Coin-like lesion in the left fourth anterior interspace due to pulmonary arteriovenous fistula. (Roentgenogram taken in the inspiratory position). (B) Same patient with roentgenogram taken in the expiratory position. Note the difference in position and density of the lesion. (C) Lateral view showing the anterior location of the lesion.

The chest x-ray film revealed a pulmonary infiltrate which pulsated and decreased in size with the Valsalva maneuver. Angiocardiography confirmed the vascular nature of the lesion.

Case 4: (Fig. 4) The chest roentgenogram shows a coin lesion due to tuberculosis which is similar in appearance to the lesion seen in Figure 3. The calcification in the lesion suggested the inflammatory nature of the density. The patient had a positive tuberculin test, but negative skin tests for histoplasmosis and coccidioidmycosis.

Case 5: (Fig. 5) This 36 year-old man gave a history of cough, dyspnea, and blood-streaked sputum of several months' duration. Telangiectatic lesions on the lips and tongue had been present for many years.

The chest x-ray film showed bilateral hilar prominence, particularly on the left where a density extended peripherally into the lung parenchyma. At thoracotomy, bronchogenic carcinoma was found.

Comments: The differential diagnosis of pulmonary infiltrate seen on chest x-ray film includes many of the diseases which may present as "coin lesions." These include carcinoma, granuloma, hamartoma, fibroma, adenoma, bronchial cyst, etc. (Figs. 3 to 5). It is surprising that most reports of large series of coin lesions make no mention of pulmonary arteriovenous fistulae[20-23] for the faint vascular opacities leading to the lesion might easily be missed, leaving only the coin lesion appearance of the fistula itself.

Case 6: This man, aged 28, gave a history of hemoptysis of three days' duration. In addition, he noted dyspnea, cyanosis, and digital clubbing for the past three years. He also complained of weakness and occasional attacks of dizziness.

The chest x-ray film demonstrated the typical roentgenographic findings of arteriovenous fistula. The large expansile mass in the lower lobe and the increased density of the hilar regions on the involved side are characteristic.

The diagnosis was confirmed at operation. The hemoptysis was caused by rupture of the fistula with pulmonary parenchymal hemorrhage.

Case 7: (Fig. 6) This was a 21 year-old man who had recurrent pneumonia and hemoptysis. Roentgenograms showed a resolving right lower density similar to the lesion in Case 6. In this instance, the infiltrate was caused by bronchiectasis.

Case 8: (Fig. 7) This patient with tuberculosis developed digital clubbing and cyanosis. The cyanosis and clubbing gradually increased. The red cell count rose to 6.8 million/mm.^{3} and the hemoglobin to 19 Gm. per cent. Thoracotomy was performed. Several tuberculomas were found at the left apex. In addition, fistulae were also found in the upper portion of the left lower lobe posteriorly. The patient had coexistent tuberculosis and pulmonary arteriovenous fistulae.

Comments: Tuberculosis has not infrequently been confused with arteriovenous fistulae in the past. However, O'Rourke[24] reported a case of pulmonary tuberculosis in which a left lower lobe resection revealed a calcified tuberculoma immediately adja-

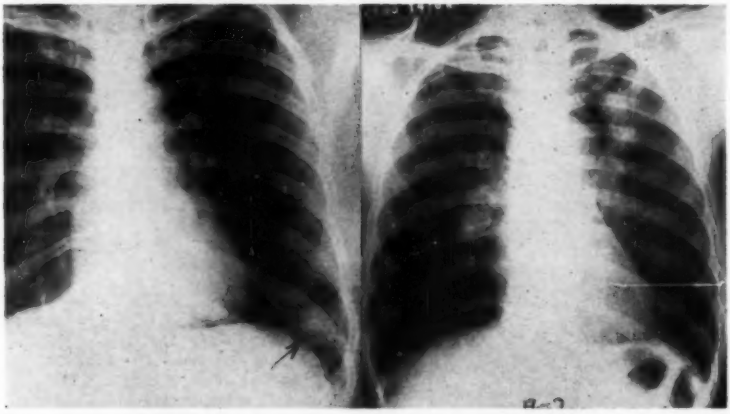

FIGURE 4 FIGURE 5

FIGURE 4 (Case 4): Coin-like lesion due to tuberculosis (tuberculoma). The presence of calcification suggests that the lesion is most likely inflammatory in nature.
FIGURE 5 (Case 5): Dense pulmonary infiltrate at the left apex with extension to the hilar area suggestive of vascular connections. These proved to be peribronchial infiltrates due to bronchogenic carcinoma.

cent to a large arteriovenous fistula. Thus, even in the presence of known tuberculosis, the development of cyanosis, clubbing or polycythemia out of proportion to the degree of pulmonary damage suggests a possible concomitant arteriovenous fistula; or as in O'Rourke's case, the failure of a parenchymal lesion to respond to therapy raises the suspicion of a complicating disease process.

Case 9: (Figure 8) This 26 year-old man had cyanosis, polycythemia, telangiectases of the skin, frequent episodes of dizziness and blurring of vision, and epistaxis. Four siblings and both parents had lesser degrees of telangiectasia and recurrent episodes of epistaxis.

The chest x-ray film revealed a round mass, 5 cm. in diameter, lying against the posterior chest wall. The initial impression was neurofibroma. However, fluoroscopy revealed slight pulsations of the mass and a decrease in size with the Valsalva maneuver. On angiocardiography, dye was seen within the mass and the communicating pulmonary vessels were visualized. Pneumonectomy was performed to remove the large arteriovenous fistula.

Comments: Patient 9 exhibited the classical findings of pulmonary arteriovenous fistula associated with hereditary hemorrhagic telangiectasia. An appreciation of the intimate relationship of these two conditions will lead to an early diagnosis of abnormal roentgenographic lesions of the lungs. The right lateral x-ray film of the chest was particularly helpful as it showed the prominent vessels extending from the mass to the hilum. Angiocardiograms confirmed the diagnosis.

Discussion

With many cases now reported in the literature, pulmonary arteriovenous fistula can no longer be considered a rare entity. Early diagnosis and treatment is facilitated by an appreciation of the typical roentgenographic appearance. In addition, a high index of suspicion will at least allow a consideration of the diagnosis in the evaluation of all pulmonary lesions. The relationship of pulmonary arteriovenous fistula to hereditary hemorrhagic telangiectasia is well documented, and all patients and relatives of patients with known pulmonary arteriovenous fistulae should be examined for the presence of telangiectasia.

With few exceptions, all pulmonary arteriovenous fistulae are of congenital or familial origin. Plastic and metal casts of resected fistulae, as well as histologic studies have demonstrated multiple small arteriovenous anastomoses suggestive of a fetal-type circulation.[16,25,26] Occasional reports of acquired arteriovenous fistulae have also appeared. A recent report concerned multiple pulmonary arteriovenous fistulae believed secondary to metastatic carcinoma of the thyroid.[27] Others have suggested acquired fistulae from pulmonary schistosomiasis[28,29] and long-standing hepatic cirrhosis.[30] At present, however, these represent a small percentage of the pulmonary arteriovenous fistulae described in the literature.

The absence of a pulmonary roentgenographic lesion, even on angiocardiographic study, does not rule out arteriovenous fistula. There are several reports of patients whose clinical picture and laboratory studies strongly suggested pulmonary arteriovenous shunting of blood though roentgenograms and angiocardiography were negative. In these instances, exploratory thoracotomy confirmed the presence of multiple minute pulmonary arteriovenous communications.[16]

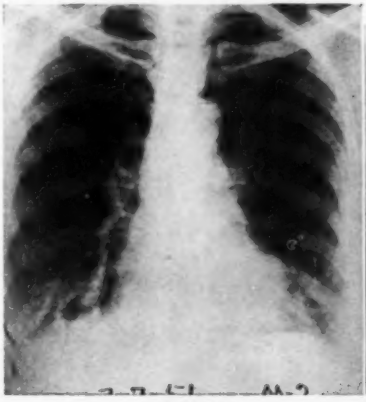

FIGURE 6

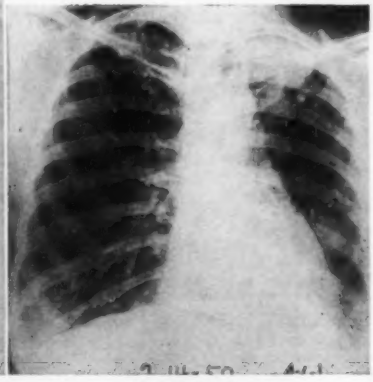

FIGURE 7

FIGURE 6 (Case 7): Bronchiectasis and pneumonic infiltration of the right lower lobe. FIGURE 7 (Case 8): Chest x-ray of patient with coexistent tuberculosis (left upper lobe) and pulmonary arteriovenous fistulae (left lower lobe).

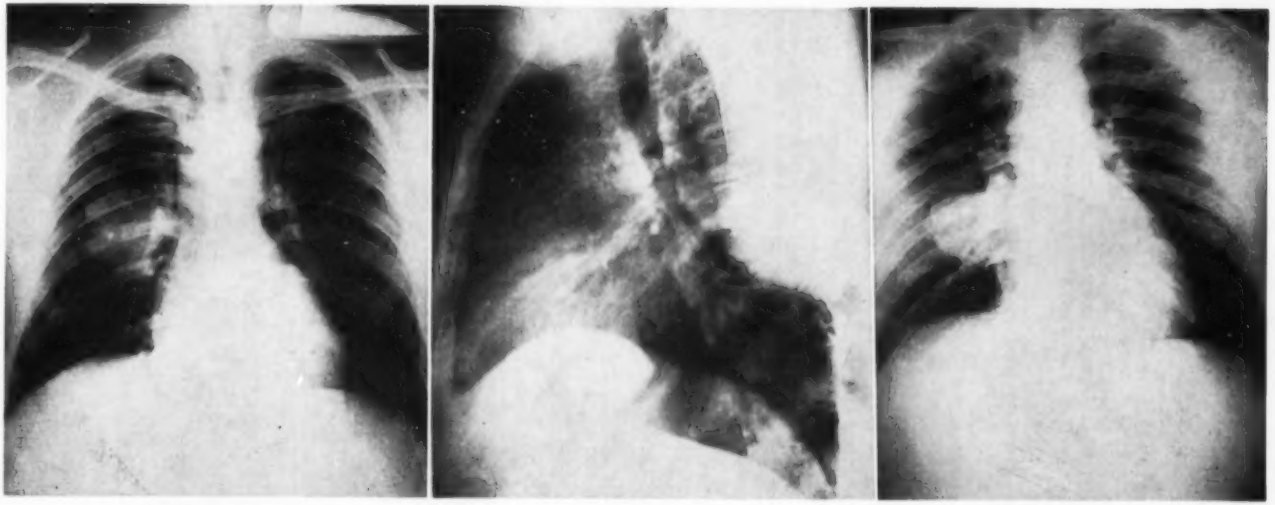

FIGURE 8A FIGURE 8B FIGURE 8C

FIGURE 8 (Case 9): (A) Chest x-ray of patient with arteriovenous fistula of the apex of the right lower lobe. This was originally diagnosed as bronchogenic carcinoma. (B) In the lateral view, the lesion is seen to be posterior. (C) Angiocardiography confirmed the vascular nature of the lesion.

SUMMARY

1. The classical findings of pulmonary arteriovenous fistulae are described.
2. The hereditary nature of the disease is emphasized.
3. The importance of the lesion in the differential diagnosis of pulmonary roentgen opacities is discussed and supplementary fluoroscopic and angiocardiographic studies are suggested.
4. In patients presenting with unexplained bleeding, cutaneous telangiectasia, or central nervous system complaints, the possibility of a pulmonary arteriovenous fistula should be considered.
5. The therapy of choice is surgical excision of the lesion, especially when the physiologic defect is severe.

RESUMEN

1. Se describen los hallazgos clásicos de la fístula arteriovenosa pulmonar.
2. Se hace resaltar la naturaleza hereditaria de esta afección.
3. La importancia de la lesión en el diagnóstico diferencial de las opacificaciones pulmonares a los rayos X es motivo de disertación y se sugieren estudios adicionales fluoroscópicos y angiocardigráficos.
4. En los enfermos que tengan un sangrado inexplicable, telangiectasia cutánea, o trastornos nerviosos, debe considerarse la posibilidad de una fístula arteriovenosa pulmonar.
5. El tratamiento de elección es la excisión quirúrgica de la lesión especialmente si el defecto fisiológico es severo.

RESUMÉ

1. Les auteurs décrivent les constatations classiques des fistules artério-veineuses pulmonaires.
2. La nature héréditaire de cette affection est mise en lumière.
3. Ils discutent l'importance de la lésion dans le diagnostic différentiel des opacités radiologiques pulmonaires, et préconisent des études supplémentaires radiologiques et angiocardiographiques.
4. La possibilité d'une fistule artério-veineuse pulmonaire devrait être considérée chez les malades atteints de saignement inexpliqué, de télangectasie cutanée, ou d'atteintes du système nerveux central.
5. Le traitement de choix est l'exérèse chirurgicale de la lésion, surtout quand le trouble physiologique est grave.

ZUSAMMENFASSUNG

1. Beschreibung der klasischen Befunde bei pulmonalen arteriovenösen Fisteln.
2. Der örtliche Charakter dieser Erkrankung wird hervorgehoben.
3. Die Wichtigkeit dieses Befundes bei der Differentialdiagnose pulmonaler röntgenologischer Verdichtungen wird besprochen und zusätzliche Untersuchungen mittels Durchleuchtung und Angiocardiografie werden vorgeschlagen.
4. Bei Kranken, bei denen eine nicht erklärbare Blutung, eine Teleangiektasie der Haut oder Beschwerden von Seiten des zentralen Nervensystems bestehen, sollte man die Möglichkeit einer arteriovenösen Fistel in der Lunge in Erwägung ziehen.
5. Die Therapie der Wahl ist die chirurgische Beseitigung der Erkrankung, besonders dann, wenn der physiologische Defekt schwer ist.

Complete reference list will appear in the reprints.

HEMODYNAMIC STUDIES IN ACUTE PULMONARY EDEMA

Hemodynamic changes are described in five patients before, during and after episodes of acute pulmonary edema. It would appear that the precipitating causes of pulmonary edema in these patients were: 1) the maintenance of a supine position for a prolonged period with redistribution of blood from the peripheral circulation to the lungs, and 2) anxiety about the procedure, causing sympathetic stimulation.

The principal findings included a marked rise in pulmonary artery and pulmonary wedge pressures, low cardiac output, increased heart rate and decreased diastolic filling period. Marked elevation of systemic blood pressure and increase in right ventricular diastolic pressure were observed in two patients. Four patients were treated wtih intravenous hexamethonium in doses ranging from 6.2 to 25 mg. and all showed a dramatic response to the drug with regression of the above changes and prompt clinical improvement.

Finlayson, J. K., Luria, M. N., Stanfield, C. A. and Yu, P. N.: "Hemodynamic Studies in Acute Pulmonary Edema, *Ann. Int. Med.*, 54:244, 1961.

The Post-Myocardial Infarction Syndrome

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In 1955, Dressler[3] described for the first time a syndrome which follows myocardial infarction and mimics the post-commissurotomy syndrome and idiopathic recurrent benign pericarditis.[4,5] Following this report, a number of papers have appeared in the literature.[1,2,6,11,12] The syndrome is usually of good prognosis, but fatal cases have been reported.[6,12] The importance of the correct diagnosis of the syndrome lies in avoiding the anticoagulant treatment which predisposes to hemorrhagic exudates and endangers life by producing cardiac tamponade.[6]

One of us has recently reported two typical cases of the syndrome[11] and the present paper is concerned with all cases observed in our department between 1954 and 1960. Furthermore, we intend to discuss a few other cases which present some fairly common manifestations associated with myocardial infarction, for which no satisfactory explanation exists to-date, and which, we suggest, should be considered as a form of the post-myocardial infarction syndrome.

Material and Methods

The records of 206 patients treated in our department from January, 1954 to June, 1960 with a diagnosis of myocardial infarction were reviewed. From these, 17 were discarded because of early death ensuing within one week from the attack of the infarction, and thus there was not sufficient time for the syndrome to develop. From the remaining 189 cases there were 29 presenting some probable manifestations of the syndrome, but from these 14 were discarded because of insufficient data of the records. From the total of 175 cases there remain, therefore, 15, including the two previously reported, which form the basis of the present discussion.

Analysis of the Cases

Our cases have been divided into three groups, which are shown in Table 1.

TABLE 1 — CLASSIFICATION OF THE CASES

Group	Number of cases	Incidence per cent
Typical cases	8	4.6
Atypical cases	4	2.3
Cases proposed as forms of the syndrome	3	1.7
Total	15	8.6

The incidence of the typical cases is 4.6 per cent but if the atypical cases and the ones which we think are forms of the syndrome are included, the incidence becomes 8.6 per cent.

From the Department of Cardiology, "Evangelismos" Hospital.

Typical Cases

All of our eight typical cases were men, but this is not statistically significant, since from the whole of the 175 cases examined there were 24 women only, due to the fact that in our department the number of beds for men is nearly double the number of beds for women. Six of the eight cases were on anticoagulant treatment when the syndrome appeared, but we cannot make any implication of this, because in our department anticoagulant treatment is applied routinely in all cases of myocardial infarction, except the ones for which special contraindications exist.

To the following description of the syndrome, we added two more typical cases, selected from the private practice of one of us, thus making a total of ten cases.

The age distribution was as follows:

3 cases between 41 — 50 years
4 cases between 51 — 60 years
3 cases between 61 — 70 years

The site of the infarction is shown in Table 2.

TABLE 2 — LOCALIZATION OF THE INFARCTION IN TEN TYPICAL CASES

Site of infarct		Total number of cases	
Anterior infarcts	Anteroseptal	1	
	Anterior	1	5
	Antero-lateral	3	
	Inferior wall	3	
Posterior infarcts	Postero-lateral	1	4
Both anterior and posterior infarcts		1	1
	Total	10	10

As one can see, there was about an equal number of anterior and posterior wall infarctions.

The time of appearance of the syndrome in relation to the attack of the infarction is shown in Table 3.

TABLE 3 — APPEARANCE OF THE SYNDROME IN RELATION TO THE INFARCTION

Time	Number of cases	Remarks
Six weeks before the attack of infarction	1	He has had attacks of angina some months before the infarction
First week after	1	
Third week after	2	
Fifth week after	2	
Sixth week after	1	
Eighth week after	1	
Ninth week after	1	
Undetermined	1	

From this table it is apparent that the syndrome may begin as a continuation of the fever of the infarction, i.e. within the first week, and as long as two months after the initial attack. It will be noted that in one case the syndrome began before the attack of the infarction, when only attacks of angina were present. Six weeks before the infarction the

TABLE 5—CLINICAL PICTURE OF 10 TYPICAL CASES OF POST-MYOCARDIAL INFARCTION SYNDROME

Cases	Age	Site of the Infarct	Time of Appearance in Relation to the Infarction in Weeks	Number of Attacks	Clinical Features											Laboratory Findings										
							Pleural Effusion			Pericarditis			Pain Elsewhere Than Thorax							Blood			Pleural Effusion				
					Fever	Pain of Pleuro-pericardial Type	Right	Left	ECG Signs	Pericardial Effusion	Cardiac Tamponade	Diffuse Pain in the Abdomen	Diffuse Joint Pains and Aches	Anemia	Pneumonitis	Erythrocyte Sed. Rate Increased During Paroxysms	Erythrocyte Sed. Rate Increased Between Parox.	Eryth. Sed. Rate Hi After Other Symptoms Subsided	Leucocytosis+. Shift to the Left	C-Reactive Protein	Blood Eosinophils Increased	Grossly Hemorrhagic	Erythrocytes Found on Microscopic Examination	Polymorphonuclears Predominate	Protein Increased	Eosinophils Found
Case 1	60	Antero-lateral	9th	More than 5	+	+	−	+	−	−	−	−	— No information	−		+	+	+	+	Not examined	No information	−	No information			
Case 2	65	Inferior wall	3rd	2	+	+	+	−	−	−	−	−	−	+	+	+	No information		+	Not examined	−	−	+	+	+	+ 10%
Case 3	56	Antero-lateral	8th	5	+	+	−	+	−	−	−	−	−	+	−	+	+	−	+	Not examined	−	−	+	+	+	−
Case 4	46	Antero-septal	undetermined	2	+	+	−	−	−	−	−	−	−	−	−	+	−	+	−	Not examined	−	−	−	−	−	−
Case 5	62	Inferior wall	6 weeks before	More than 5	+	+	−	−	+	−	−	−	+	−	−	+	+	+	−	+	−	−	−	−	−	−
Case 6	68	Antero-lateral	1st	More than 5	+	+	+	−	−	+	+	−	−	+	−	+	+	−	+	+	−	+	+	+	+	−
Case 7	56	Inferior and Antero-lateral	3rd	4	+	+	−	+	−	+	+	−	−	+	−	+	−	−	+	+	From 0 to 5%	−	+	+	+	−
Case 8	42	Postero-lateral	5th	3	+	+	−	−	+	−	−	+	−	+	−	+	+	+	+	+	−	−	−	−	−	−
Case 9	46	Anterior	5th	1	+	+	−	+ Friction only	−	−	−	−	−	−	−	+	−	−	+	Not examined	From 0 to 6%	−	−	−	−	−
Case 10	57	Inferior	6th	1	+	+	−	−	−	−	−	−	−	−	−	+	−	+	+	Not examined	−	−	−	−	−	−
Total	—	—	—	—	10	10	2	4	2	2	2	1	1	5	1	10	5	5	8	4	2	1	4	4	4	1

patient began to experience pains of the pleuropericardial type, associated with low grade fever. Erythrocyte sedimentation rate was 100-120 mm./hour. The course of this case after the infarct was typical of the post-myocardial infarction syndrome. Table 4 shows the number of the attacks of the syndrome in each case.

TABLE 4

Number of attacks	Number of cases
1	2
2	2
3	1
4	1
5	1
More than 5	3
Total	10

There were two cases with a single attack, but four had five or more. In one of those the syndrome was going on for one and one half years and in another it is still going on with remissions and relapses, four and one half years after the attack of the myocardial infarction. The clinical picture of the ten typical cases is shown in Table 5.

Most constant findings are fever, pain of pleuropericardial type and increased sedimentation rate, occurring in all of the cases, followed by leucocytosis, occurring in eight of ten cases, and the least common is pneumonitis, whereas overt signs of pleural and/or pericardial affection occupy an intermediate position. Of the six cases in which there was a pleural reaction, in three there was a left sided effusion, in two a right sided one, and in one a left sided friction only. The effusion was grossly hemorrhagic in one case, and straw colored in the remainder. Information about the miscroscopic examination of the effusion in one case is not available. In the remaining four, microscopic examination revealed erythrocytes to be always present. The effusion was an exudate in all cases. Polymorphonuclears predominated, but in one case, in a second tapping lymphocytes predominated. In one case, 10 per cent of eosinophils were found in the effusion. Blood eosinophilia was noted in two cases. Pericardial effusion, producing cardiac tamponade was present in two cases, but in another two cases there was waxing and waning ST-T depression, suggesting of pericarditis. In no instance was pericardial tapping performed. Anemia was present in five cases, and as noted by others,[5] it was usually associated with a protracted course. The erythro-

TABLE 6

Course of the erythrocyte sed. rate	Number of cases	Remarks
Increased during the paroxysms only	3	In one case it was not subsequently followed
Increased during and between the paroxysms but fell subsequently to normal	2	
Increased during the paroxysms only but remained high after the last one	2	
Increased both during and between the paroxysms and remained high after all other symptoms subsided	3	

cyte sedimentation rate was followed by serial examination in nine of the ten cases. Its course is shown in Tables 6 and 7.

It is seen that the erythrocyte sedimentation rate may remain high between the paroxysms and long after them.

TABLE 7

Course of erythrocyte sedimentation rate	Cases with more than 3 paroxysms	Cases with less than 2 paroxysms	Total number of cases
Increased between the paroxysms	5	0	5
Normal between the paroxysms	1	3	4
Total	6	3	9

Of the five cases in which the erythrocyte sedimentation rate remained high after each paroxysm, there were three or more attacks. Conversely, of six cases with more than three attacks, in five the sedimentation rate was increased during the paroxysms. The significance of the above finding will be discussed later.

Atypical Cases

There were four cases, three men and one woman, which were characterized as atypical. The clinical features and laboratory findings of these cases are shown in Table 8.

TABLE 8 — ATYPICAL CASES

Cases	Sex	Age	Site of infarct	Appearance after infarct	Attacks	Pains pleuro-peric. type	Fever	Shoulder perie-arthr.	Sed. rate incd during attacks	Sed. rate increased between attacks	Sed. rate increased after all symptoms subsided
1	M	45	Inferior wall	3rd week	1	+	−	+	+	−	−
2	M	53	Inferior wall	3rd week	2	+	−	−	+	+	+
3	F	58	Antero-septal	3rd week	2	+	−	−	+	−	−
4	M	52	Inferior wall	2nd week	2	−	+	−	+	+	+

Three of the cases presented pain of pleuropericardial type and increased sedimentation rate, and in one of them there was an attack of right shoulder periarthritis 12 days after the ensuing of the pleuropericardial pain. The fourth case had two attacks of fever associated with increased sedimentation rate without any apparent explanation. Although these cases do not present the complete picture of the syndrome, we feel that the pleuropericardial pain and increased sedimentation rate in the three cases, and the unexplained bouts of fever with increased sedimentation rate in the fourth case should very likely be attributed to it.

Cases Which We Propose to Be Considered as Form of the Syndrome

Among the 175 cases of myocardial infarction examined, there were three men, with an increased sedimentation rate long after the attack of infarction, which exhaustive clinical and laboratory examinations

could not explain. In two cases the initially high sedimentation rate was due to the infarction having fallen and there was a considerable increase again up to 40 mm./hour in the third and fifth week respectively, which remained high until the day of their discharge two and one-half months and one month after the second increase, respectively. In the first case there was a transient leucocytosis with a shift to the left and an increase of the eosinophils from zero to five, with simultaneous increase in the sedimentation rate. The second had not had leucocytosis but an increase in the number of eosinophils up to 7 per cent was noted.

The third case has had a persistence of the initially increased sedimentation rate until the date of his discharge, two months after the infarction. No follow-up was made in these cases.

Discussion

Although our results suffer from the disadvantages of a retrospective study, we think that some useful conclusions may be drawn. The incidence of typical cases in this study is estimated to be 4.6 per cent, but if the atypical cases, as well as the ones presenting unexplained increased sedimentation rate are included, it becomes 8.5 per cent. The true incidence may be still higher as the milder and the atypical cases most likely go unrecognized.

It has been suggested recently[3] that serous membranes other than the pleura and pericardium might be affected. Dressler[5] reported a fatal case in which hemoperitoneum associated with hemopericardium and hemothorax was found on necropsy. Broch[2] reported two cases with knee and elbow joint affection with increased sedimentation rate and he thinks that these cases are probably examples of the post-myocardial infarction syndrome. In two of our ten typical cases there were pains in the joints or abdomen. In the light of Dressler's findings and of Broch's considerations, the pain in these cases should be explained as due to peritoneal and articular serous membrane affection. In one of our four "atypical" cases, there was a right shoulder periarthritis 12 days after an attack of pleuropericardial pain associated with increased sedimentation rate. As the affection of other serous membranes seems to be proved, it is probable that the shoulder periarthritis in this case was related to the post-myocardial infarction syndrome. It is on this ground that we agree with Broch[2] that the shoulder periarthritis syndrome following, or sometimes preceding an attack of myocardial infarction, should be considered as a form of the post-myocardial infarction syndrome, inasmuch as no other satisfactory explanation exists.

It will be recalled that in one of our cases there was pain of pleuropericardial type, low grade fever and increased erythrocyte sedimentation rate six weeks before the attack of infarction when only attacks of angina were present. Following the infarction there was a typical protracted course of post-myocardial infarction syndrome. We believe that this case affords proof of the hypothesis that the syndrome can occur without a major infarction, but with only small areas of necrosis.

As already suggested[5] the site of the infarction plays no part in the production of the syndrome. In this series anterior and posterior infarcts were of about equal frequency. The diagnosis of the syndrome, at least of its typical forms, is easy, provided that its possibility is borne in mind. The distinction between the pain of the syndrome and an extension of the myocardial infarction should be easy, as pointed out by Dressler,[5] and McGuire and his associates[3] and whenever pericarditis is present pulmonary embolism can easily be excluded.[14]

Dressler[5] considers that the most sensitive index of complicating pleuropericarditis is the characteristic pain aggravated by deep inspiration, change of posture, yawning, coughing and rarely swallowing. In our series of ten typical cases definite signs of pericarditis were present in four and of pleural reactions, which were always unilateral, in six. The characteristic pain was present, at some time during the attacks, in all cases. Fever and increased erythrocyte sedimentation rate were always present also. Thus, the characteristic triad of the syndrome should be: fever—pain of pleuropericardial type—increased erythrocyte sedimentation rate, provided that pulmonary embolism can be excluded. This triad can be combined with pleural and pericardial effusion or fibrinous reaction, leucocytosis, anemia and pneumonitis, and has a tendency to relapses. Occasionally, pain elsewhere than the thorax can be due to affection of other serous membranes. C-reactive protein seems to be a common finding of the attacks of the syndrome, being positive in all four cases in which it was examined. No doubt, as suggested by others as well,[1,2,9] the syndrome may occur in atypical forms, when only one or two of its features are present. Bouvrain[1] wonders if the prolonged fever after a myocardial infarction is a form of the syndrome. Considering the above views, we feel that the inclusion in the syndrome of our "atypical" cases, which were characterized by bouts of pain of pleuropericardial type, or unexplained fever, all associated with an increased sedimentation rate, is justified.

If erythrocyte sedimentation rate is considered alone, it presents some interesting aspects. It remained high between the paroxysms in five cases, and all of those had a protracted course. Conversely, of six cases with a protracted course only one had a normal sedimentation rate between the paroxysms. It seems, therefore, that persistence of an increased sedimentation rate after a paroxysm heralds relapses. On the other hand, the erythrocyte sedimentation rate remained high after all other manifestations of the syndrome subsided in five cases. We did not follow up these cases, to see if a relapse would occur, but it seems reasonable to conclude, as noted by Dressler[3] that in these cases the persistence of an abnormal sedimentation rate constitutes the only manifestation of activity of the syndrome.

It is in relation to this finding that we propose that our three cases with the only abnormal manifestation the unexplained high sedimentation rate, long after the attack of the myocardial infarction, should be included in the post-myocardial infarction syndrome. Indeed, every cardiologist having treated a sufficient number of myocardial infarctions has encountered such cases of prolonged high sedimentation rate at a time when it cannot possibly be accounted for by the myocardial infarction *per se*, and for which detailed clinical, x-ray, electrocardiographic and laboratory examinations fail to give a satisfactory explanation. We strongly feel that these cases constitute an atypical, monosymptomatic manifestation of the post-myocaradial infarction syndrome.

The etiology of the syndrome is as yet unknown. It has been indicated by Dressler[3] that autosensitization takes place from antigen produced by the myocardial necrosis and Nicolay[10] suggests that an adrenal-pituitary dysfunction might play a part as well. In two of our ten typical cases, eosinophilia was present during the paroxysms. This finding was also noted by Dressler[3] and by Bouvrain and associates.[1] In another case of ours, eosinophilia up to 10 per cent was present in the pleural effusion. In two of the three cases in which increased sedimentation rate was, as we believe, the only manifestation of the syndrome, an increase in the number of blood eosinophils was noted, coincident with the increase in the sedimentation rate. The above findings support Dressler's view that the syndrome is due to autosensitization.

Dressler[3] pointed out that corticosteroids have a dramatic beneficial effect, but on withdrawal, relapses occur commonly.[6] In one of our cases, corticosteroids were given after many relapses, with an immediate disappearance of all manifestations. On withdrawal there was no relapse up to two and a half years when we last contacted the patient. Dressler recently reported a similar case.[7]

SUMMARY AND CONCLUSIONS

In a retrospective study of 175 cases of myocardial infarction, ten typical cases and four atypical ones of post-myocardial infarction syndrome were found and described. In addition, three more cases presenting unexplained increase of the erythrocyte sedimentation rate many weeks after the infarction are presented. Two typical cases presented evidence of joint and peritoneal involvement apart from the pericardium. An atypical case presented an attack of shoulder periarthritis. In relation to these, the opinion is expressed that the shoulder periarthritis asociated with myocardial infarction must be considered as a form of the post-myocardial infarction syndrome. Findings supporting the view of the autosensitization nature of the syndrome are presented. The idea is put forward that unexplained increase in the erythrocyte sedimentation rate long after an acute myocardial infarction is probably a monosymptomatic form of the post-myocardial infarction syndrome.

RESUMEN

En un estudio retrospectivo de 175 casos de infarto del miocardio, diez casos típicos y cuatro atípicos del sindrome de infarto postmiocardiaco se encontraron y son descritos. Además, se presentan tres casos mas, de aumento de la velocidad de la eritrosedimentación muchas semanas después del infarto, sin explicación. Dos casos típicos presentados hacen evidente el compromiso articular y peritoneal ademas del pericárdico. Un caso atípico presentó un ataque de periartritis del hombro. En relación con estos, se expresa la opinión de que la periartritis del hombro asociada al infarto del miocardio debe ser considerada como unaforma del sindrome de infarto postmiocárdico. Se presentan hallazgos que soportan el concepto de que el sindrome corresponde a una autosensibilización. Se adelanta la idea de que un aumento inexplicable de la eritrosedimentación mucho después del infarto agudo del miocardio es probablemente una forma monosintomática del sindrome de infarto postmiocárdico.

ZUSAMMENFASSUNG

Bei einer retrospektiven Untersuchung an 175 Fällen von Herzinfarkt fanden sich 10 typische und 4 atypische Fälle von Post-Myocard-Infarkt-Syndrom, die beschrieben werden. Außerdem wird über drei weitere Fälle von ungeklärtem Anstieg der Blutkörperchensenkungsgeschwindigkeit viele Wochen nach dem Infarkt berichtet. Zwei typische Fälle boten Anhaltspunkte von Beteiligung von Gelenken und Bachfell abgesehen vom Herzbeutel. Ein atypischer Fall zeigte eine Attacke einer Periarthritis der Schulter, Es wird in Bezug auf letztere die Meinung ausgesprochen, daß die Periarthritis der Schulter in Verbindung mit einem Herzinfarkt als eine Form des Post-

Myocard-Infarkt-Syndromes angesehen werden muß. Die die Auffassung der autosensibilisierenden Natur des Syndroms unterstützenden Befunde werden dargelegt. Es wird die Meinung vorgebracht, daß ein ungeklärter Anstieg der Blutkörperchensenkungsgeschwindigkeit lange Zeit nach einem akuten Herzinfarkt wahrscheinlich eine monosymptomatische Form des Post-Myocard-Infarkt-Syndromes bedeutet.

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PULMONARY ARTERY PRESSURE

During cardiac catheterization, pulmonary and systemic arterial pressure, arterial oxygen saturation, respirations, and heart beats were recorded continuously during the change from breathing air to breathing 95 to 99.5 per cent oxygen in a series of 31 patients with ventricular septal defect. In addition, pulmonary and systemic blood flows were measured under the two circumstances.

Systemic arterial oxygen saturation began to increase about five seconds after the change from breathing air to breathing oxygen. Within a few seconds thereafter, the pulmonary artery pressure and heart rate began to decrease. After approximately three minutes, the changes in these parameters appeared essentially complete.

The pulmonary blood flow increased by an average of 32 per cent while systemic flow decreased by 15 per cent during breathing of the high oxygen mixture. The average calculated pulmonary pressure: flow ratio (resistance) was decreased by 36 per cent while the average systemic pressure/flow ratio was increased. The occurrence of these changes was independent of the presence of pulmonary hypertension, of the use of general anesthesia, and of the age of the patient.

The authors conclude that in patients having ventricular septal defects, the presence of vasomotor tone in the pulmonary vasculature is usual, and that in those having associated pulmonary hypertension, a significant contributing factor is constriction of the precapillary pulmonary resistance vessels.

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SUMMARY OF CURRENT THERAPY

Edited by Eliot Corday, M.D.

Therapy of Hypotension in Acute Myocardial Infarction

E. MAURICE HELLER, M.D.*
Toronto, Ontario

Hypotension occurs in about 10 per cent of patients with acute myocardial infarction, and if not quickly reversed, may result in a mortality rate of 80 per cent or higher.[1] The drop in pressure is probably due to the inability of the left heart to maintain an adequate output (cardiogenic shock), as well as to failure of peripheral response. The most important therapy is immediate oxygen administration and other symptomatic measures, together with adequate morphine, (or meperidine) for complete pain relief. If patient is not in hospital, emergency admission, with oxygen therapy en route, is mandatory. There is no longer any doubt that levarterenol (Levophed), also known as 1-noradrenaline and 1-norepinephrine, has saved the lives of many patients after severe myocardial infarction complicated by acute hypotension.[2]

The use of levarterenol as a means of raising the systemic blood pressure during hypotension of varying origin has become widely adopted, and has the advantage over the use of other drugs of being strictly physiologic.[3,4] This sympathomimetic primary amine slows the pulse rate and increases total peripheral resistance by causing generalized vasoconstriction of arteries, capillaries and veins (although it produces coronary vasodilatation).[3] Thus the blood pressure is elevated and the mean aortic pressure rises, producing a proportionate increase of coronary flow while at the same time there is a greater effective glomerular filtration pressure and an increase in urinary output.[5] Because of the increase in pulmonary arterial, capillary and venous pressures, the possibility of aggravating or producing pulmonary edema must be considered, especially in patients who already have congestive heart failure. Levarterenol does not produce central nervous system stimulation and tachycardia with the associated anxiety, discomfort and peculiar feelings that follow administration of epinephrine (adrenaline). It is also eight times less toxic.

The evanescent effect of levarterenol makes it the safest vasopressor drug. Compare this to the so-called simpler intramuscular medications (such as mephentermine) which may result in an action up to two hours and cannot be stopped promptly if for example, an arrhythmia occurs—this rarely happens as a result of vasopressor agents unless the blood pressure is raised too high.[6] As a matter of fact, levarterenol may successfully *terminate* arrhythmias that are not infrequently associated with hypotension (such as premature systoles, atrial and ventricular tachycardias, atrial fibrillation, sinus bradycardia and heart block), or it may serve to correct the severe hypotensive state until quinidine or other anti-arrhythmic agents revert the rhythm to normal.[6]

Hypotension going on to shock (following myocardial infarction) may be partly or entirely due to other factors which should be thought of and

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treated at the same time that levarterenol therapy is begun. These include severe congestive heart failure, heart block, ventricular or supraventricular arrhythmias with tachycardia, diabetic acidosis, hemorrhage, infection, pulmonary infarction, cerebrovascular accident, hypotensive drugs, or even morphine sulfate itself.

Levarterenol is indicated in both high and low venous pressure types of shock but digitalis should also be given (and may be life-saving) when, as so often happens, definite congestive failure is also present.[7,8]

Indications for Levarterenol

It is important to begin levarterenol therapy at the proper time. When the blood pressure falls below 80 mm. Hg. systolic, the patient usually dies and the longer the delay in instituting adequate levarterenol therapy, the less the chance of survival.[7] Therefore, the author feels that one should not wait for the actual *signs* of shock. If the systolic blood pressure remains under 80 to 85 mm. Hg. (or under 90 to 95 mm. in a known hypertensive) in spite of oxygen and adequate morphine (or meperidine) for from one to three hours, levarterenol should be started.

If clinical evidence of peripheral vascular collapse is present (and not only a drop in blood pressure), levarterenol should be begun *immediately*. This is because an apparently "irreversible" state may develop after several hours or sooner, but if the blood pressure is artificially maintained with levarterenol (even for days) the condition is more likely to become self-correcting, i.e. reversible.[1] Systolic ballooning of the ventricular myocardium seems to be related to shock and is corrected by relief of the shock.[15] If the latter is associated with coronary pain only, it is of the mild type, and some authorities[8] suggest delaying levarterenol therapy to see if the shock is reversed by the relief of pain. However, we feel that it is wiser to wait no longer than the time it takes to get the drug ready for administration.

Levarterenol Administration and Dosage

Four cc. (one ampoule) of levarterenol bitartrate is added to 1000 cc. of 5 per cent dextrose in distilled water. The levarterenol solution should be started at seven to ten drops per minute and gradually increased to 60 drops per minute if necessary to keep the systolic blood pressure over 100 mm. Hg. (over 110 if the patient has been hypertensive). If a rate exceeding 60 drops per minute is required, another ampoule of levarterenol should be added. If the desired response is going to be obtained with a certain strength of solution, it is usually instantaneous, and much valuable time is lost if there is any delay before increasing the concentration. If heart failure is present, it is preferable, for example, to give three ampoules at 20 drops per minute rather than one ampoule at 60 drops per minute; that is, the infusion volume should be reduced by increasing its concentration.

Levarterenol therapy is not enough. We must give *adequate* levarterenol therapy. The best guide to dosage is careful observation of the patient and, more particularly, the blood pressure. The urinary output reflects the response of the kidney to shock and is a great aid in determining the severity of the hypotension as well as in evaluating therapy and prognosis. Usually one ampoule of levarterenol suffices, but in the more severe cases we have found[9] that the concentration must be in-

creased four to six-fold or more before an adequate rise in blood pressure is maintained. It should not take more than 15 to 20 minutes to reach this concentration (which, if required, makes the prognosis worse).

If extravasation occurs, it should be treated immediately and the infusion changed to another vein. Local tissue sloughs sometimes result from infiltration when the intravenous drip is being started. Accordingly, the bottle containing levarterenol should preferably be attached only after free flow has first been established with a 5 per cent solution of dextrose in water. (From the onset of therapy it is advisable to use a Y-tube and two bottles to facilitate changes in concentration.) The best therapy for extravasation is immediate subcutaneous injection with a hypo needle into the involved ischaemic area of 10 to 15 cc. saline solution with a few cc. of 2 per cent xylocaine (to relieve the great amount of pain usually present[10]) and 5 mg. of phentolamine hydrochloride (Regitine).[11] If injected within two to four hours, this will prevent tissue necrosis, which might otherwise be extensive—a reflection of levarterenol's extreme potency as a vasoconstrictor agent. The saline dilutes the levarterenol while the phentolamine presumably blocks its action on adrenergic effector cells, preventing necrosis by decreasing its marked vasoconstrictor effect. We have routinely been adding 5 mg. of phentolamine to each 1000 cc. of infusion fluid with excellent results since Zucker *et al.*[12] showed that this prevented necrosis in areas of extravasation without impairing the hypertensive effect. In each levarterenol flask we also include 20 mg. (2000 units) of heparin, since this may usually prevent thrombosis in the infused vein and perivenous reactions and necrosis which some patients tend to develop.

The intravenous needle should be well advanced into the vein and securely fixed, but in all cases in which several days of therapy are contemplated, it is advisable to cut down on the vein and insert a small polyethylene tube for a distance of 6 to 8 inches. In several of our patients in whom all the peripheral veins were no longer suitable or had collapsed, our surgical confrere cut down on the femoral vein; in this way therapy can be continued and the patient given renewed hope.

Although one to six days is the average, some of our patients required two to three weeks of levarterenol therapy.[2] As the blood pressure improves, the concentration should be gradually reduced and followed by a very slow drip of 5 per cent dextrose in water for a further 6 to 12 hours. Thus, if the pressure drops again (which it commonly does), levarterenol can be readministered without delay.

Special Supervision

A private nurse should constantly be present when a patient is receiving levarterenol therapy, not only to watch for extravasation, but because blood pressure readings should be made every few minutes at first and then every 10 to 20 minutes. The physician should explain the import ance of increasing or decreasing the concentration, depending on the response of the blood pressure. The nurse has not been properly instructed if she reports the systolic reading under 100, and is not increasing the drop rate or concentration.

Provided the patient can be watched carefully, there is no reason for withholding this life-saving drug. The floor nurse or intern should sit with the patient until the private nurse arrives.

Results and Comments

An excellent review from the Michael Reese Hospital, Chicago[7] exemplifies the usual response. Of 55 patients with *severe* shock after myocardial infarction treated with levarterenol, there was a mortality of 49 per cent, representing a marked improvement over the known grave prognosis of cardiogenic shock not treated with vasopressor drugs. The duration of shock, as expected, influenced the results of treatment. Of ten patients in whom the shock was known to have been present for four hours or longer when treatment was begun, only three recovered, while ten of 17 patients treated when the shock was present for less than one hour survived.

The remarkable recovery of a 62 year-old woman was reported by the author.[10] She presented with extensive acute myocardial infarction, secondary shock and congestive heart failure. Levarterenol was given for 21 days and had to be increased to a concentration of seven ampoules per 1000 cc. This case was quoted[13] as almost twice the highest concentration (with recovery) previously reported in the literature. It must be noted, however, that in over half a dozen patients given high concentration (such as six ampoules per 1000 cc.) there was no improvement; in such cases, when autopsies were obtained, extensive infarctions were found.[9] One of our patients had an excellent blood pressure response with six ampoules of levarterenol per 1000 cc.; however, one day later he succumbed. Postmortem examination showed pulmonary congestion as well as extensive acute cardiac infarction. This further emphasizes the fact that the patients in whom increased dosage of levarterenol is necessary are those in whom cardiac damage is greatest and heart failure more likely to develop. Thus, in order to obtain the necessary effect with the smallest amount of fluid, one should continue increasing the concentration of levarterenol without hesitation.

Findings elsewhere[4] are in accord with our experience that all other vasopressor agents including metaraminol and mephentermine sulfate have been far less effective. In several such cases of apparent "irreversible shock," the subsequent institution of levarterenol resulted in immediate (and permanent) improvement.[2]

The many patients who have recovered following levarterenol therapy are living proof of its great value in spite of a few instances[14] of unexplained autopsy findings, particularly focal myocarditis and hemorrhagic lesions of the pericardium and endocardium following this drug (as well as other vasopressor agents). This complication is extremely rare when one considers the large numbers given the drug and those patients would probably have died in any case.

CONCLUSION

The most important therapy of hypotension in acute myocardial infarction (next to analgesia and oxygen) is levarterenol. A specific routine is outlined which has proved to be life-saving.

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ELECTROCARDIOGRAM OF THE MONTH

Edited by Stephen R. Elek, M.D.

Intermittent Bundle Branch Block

RAY H. ROSENMAN, M.D.*
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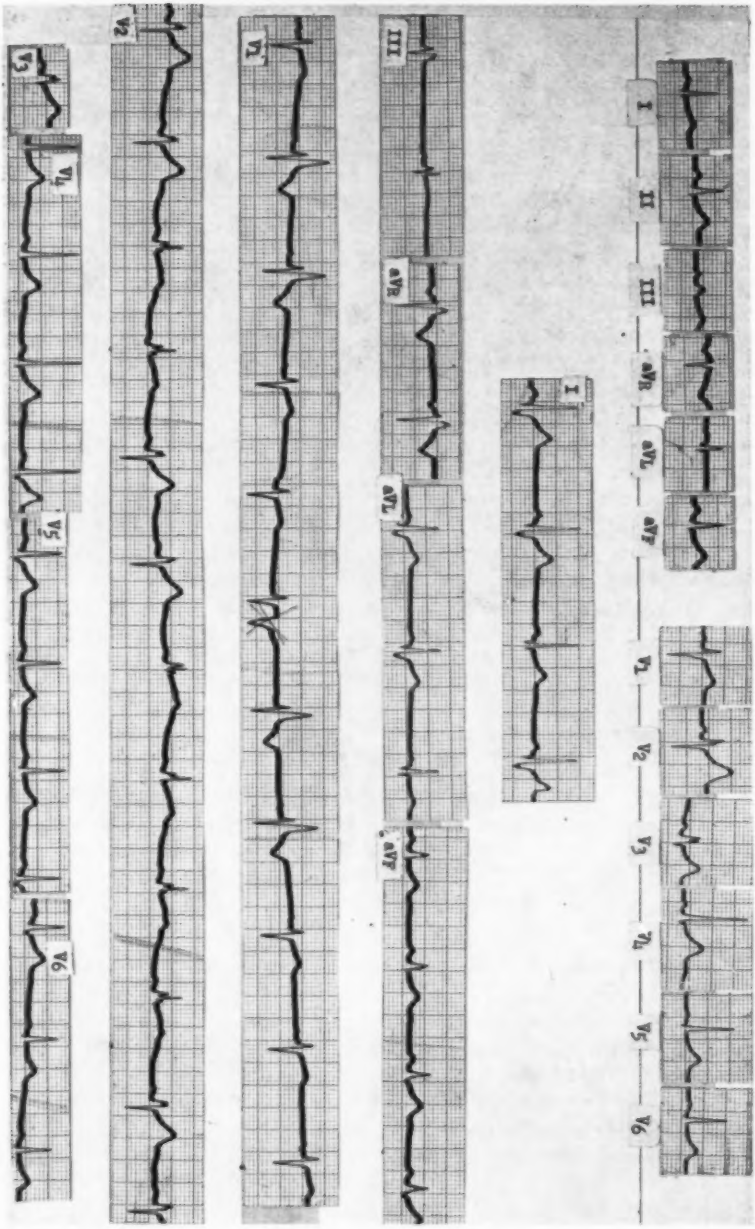

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The tracings were obtained from a 37 year-old white man, business executive, with a history of classical angina pectoris for three years and of "skipped" heart beats during exertion for one year. There is a parental history of diabetes and heart disease. The only noteworthy findings from physical examination were moderate arteriosclerotic changes in the retinal vessels and a well developed arcus senilis. No abnormality was noted in routine blood or urine analyses, or in radiologic examination of heart and lungs. The serum cholesterol ranged from 191 to 226 mg./100 ml. in six samples obtained over a 12-month interval.

The first tracing exhibits a regular sinus rhythm and normal complexes, a finding observed on one of the six occasions when tracings were obtained during 15 months of observation. The lower tracing (lead 2 omitted) exhibits the usually observed pattern of an intermittent right-sided intraventricular conduction defect. The occurrence of delayed or blocked conduction intermittently in the right main bundle branch was never noted to occur as a result of any change in the pacemaker rate or phase of respiration, and a similar pattern to that illustrated has occurred at rates varying from 60 to 100 per minute. On one occasion, at a sinus rate of 74 per minute, every complex exhibited the conduction defect. At various times occasional A-V nodal premature beats also have been noted.

Interpretation

A vagal role is probably ruled out by the absence of any relation to change of heart rate or respiration and the occurrence of intermittent conduction defect both at slow and more rapid pacemaker rates. Although Lewis initially found no histologic lesions in the conduction system in such cases and thus blamed the intermittent defect on "fatigue" of the conduction system, he recognized its relationship to organic heart disease. The appearance of intermittent bundle branch block often precedes its later permanent occurrence and is usually a manifestation of coronary heart disease.

Conclusion

The occurrence of such intermittent conduction defects, in the absence of rheumatic heart disease, thyrotoxicosis, or myocarditis, presumably should be considered a clinical manifestation of coronary heart disease, even in the absence of other clinical manifestations.

The Committee on Electrocardiography and Vectorcardiography welcomes comments. We should also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

Recommended Procedures for the Practical Evaluation of Impaired Lung Function in Individuals with Occupational Chest Diseases*

REPORT OF THE COMMITTEE ON OCCUPATIONAL DISEASES OF THE CHEST
and COMMITTEE ON PULMONARY PHYSIOLOGY
American College of Chest Physicians

Practical evaluation of lung function is feasible through the utilization of information obtained from the history, examination of the patient, and from laboratory aids that are readily available, inexpensive, and easy to perform. All functions of the lung cannot be measured by these techniques, but a fair estimate of ventilatory insufficiency can be made. Evaluation of disturbances in the respiratory gas exchange involves more detailed procedures.

This outline is general in nature with no attempt to delineate procedures in fine detail. Methods are listed by which patients with suspected occupational pulmonary disease may be studied. The extent to which various clinical and laboratory measurements are carried out and the significance of results of any particular procedure are left to the discretion of the examining physician.

The basic studies required can be divided into two broad groups: I—Clinical, and II—Pulmonary function tests.

I. Clinical

A. HISTORY

1. *Medical*

A detailed history is essential, but inquiry should especially be made about shortness of breath (quantitative estimates of exercise tolerance are important), cough, expectoration, wheezing, chest pain, hemoptysis, edema of the ankles; the occurrence of previous illnesses, particularly respiratory; smoking habits; the presence of allergy.

2. *Industrial*

The exact type of occupation, the work stresses and environmental hazards and the duration of current and past employments in chronologic order should be recorded.

B. PHYSICAL EXAMINATION

Should be complete with emphasis on the chest. The following should be specifically recorded:

1. Inspection—rate and character of breathing at rest and on exertion, cyanosis, venous distension, clubbing of fingers. Measurements of the antero-posterior and transverse thoracic diameters and the chest expansion.
2. Palpation and percussion—abnormal vibrations with breathing vocalization, variations in resonance.
3. Auscultation—character, intensity and duration of breath sounds; presence of adventitious sounds (rales) on quiet breathing, during forced expiration and after coughing.

*Classification and quantitation of the degree of lung function impairment or disability from these procedures will be the subject of a subsequent report.

4. Other—pulse rate and character, blood pressure, heart size, rhythm, presence of murmurs or thrills, edema of ankles, liver size.

C. FLUOROSCOPY
1. Level and contours of diaphragmatic domes, range and speed of excursion; paradoxic motion, reaction to sniff test.
2. Shape, position and motion of mediastinum.
3. Orientation, spacing and motion of ribs.
4. Degree and uniformity of emptying of lungs on forced expiration.
5. Valsalva maneuver.
6. Heart size, silhouette, mobility, pulsations.

D. ROENTGENOGRAMS OF CHEST
Postero-anterior and lateral standard six-foot films in full inspiration and expiration.

E. ELECTROCARDIOGRAM
12 lead recording in recumbent posture.

F. EXERCISE TOLERANCE TEST
Pulse, blood pressure, and respiratory rate before, immediately after, and two minute after 30 step-ups on a nine inch stool (20 centimeters), in one minute. Note dyspnea time. Stair climbing may be substituted.

Additional clinical studies may be done if required:

1. *Roentgenograms*
Mid-inspiratory; obliques; mid-coronal planigrams for vascular pattern; right and left transhilar 8-10 cm. oblique planigrams for delineating and measuring the pulmonary arteries; bronchograms; regional planigrams; kymographs.
2. *Electrocardiograms*
Post-exertional electrocardiogram, correlation with electrokymograms if doubt persists.
3. *Laboratory Studies*
Erythrocyte and leucocyte counts, hematocrit, sedimentation rate, urinalysis, sputum smear and culture.

II. Pulmonary Function Tests
The basic tests involve spirometry which can be performed in most medical offices with a minimum outlay for equipment.
1. Vital capacity
2. Forced expiratory volumes (timed vital capacity) for one, two, and three seconds.
3. Maximal expiratory flow rate
4. Maximal breathing capacity

If the clinical findings and spirometric values are inconclusive, additional pulmonary function studies may be done in suitably equipped laboratories.

1. Total lung capacity, functional residual capacity, and residual volume as determined by the helium rebreathing or by the open circuit nitrogen washout methods.
2. Arterial blood gas analysis breathing room air at rest and after exercise. Oximetry may be substituted for arterial blood analysis, but will not give pH or carbon dioxide values.

3. Distribution studies by any of the following methods:
   Helium equilibrium time
   Nitrogen clearance curves
   Alveolar nitrogen after oxygen breathing

Tests that may yield precise information enabling specific qualification of the type and degree of abnormality, include:

1. Diffusion capacity determination by the carbon monoxide method
2. Gradient studies using high and low levels of inhaled oxygen
3. Lung compliance and airway resistance estimations
4. Minute ventilation, tidal volume, oxygen uptake and carbon dioxide output
5. Cardiac catheterization studies.

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SCIENTIFIC NEWS ITEMS FROM THE 27th ANNUAL MEETING

AMERICAN COLLEGE OF CHEST PHYSICIANS

Round Table Luncheon Discussions

Diagnosis and Treatment of Curable Hypertension

Moderator: Travis Winsor, Los Angeles

Panel: John P. Medelman, St. Paul
John H. Moyer, Philadelphia
Grace M. Roth, Albuquerque

The discussion by Dr. Roth dealt with pheochromocytoma. She reported an occasional instance of thoracic pheochromocytoma diagnosed as tumor in the lung, with surgical death when the correct diagnosis was unsuspected. She advised studies for pheochromocytoma when labile hypertension, tachycardia and headache are present. In sustained hypertension of short duration in a young person, the cold pressor test should be done for differential diagnosis. This test in pheochromocytoma causes the blood pressure to rise at least 20 and 30 mm. If in doubt about the result, intravenous histamine may then be given. After administration of the histamine, in a positive test, the blood pressure may fall within 30 seconds and then rise precipitously within two minutes. If the blood pressure rises to moderately high levels, phentolamine (Regitine) should then be given. Dr. Roth reported 13,800 such tests without a death, the Regitine being given through a needle already in the vein.

The value of catecholamine excretion as a test for pheochromocytoma is often confused by false positive tests from bananas, nasal drops and certain antibiotics. False negative tests may be the result of the rauwolfia series unless an interval of two weeks is allowed after stopping the drug. False negative results are usual when excretion is measured during a normal blood pressure phase.

Dr. Roth cautioned about the use of sedatives in the presence of pheochromocytoma particularly preoperatively. Sedatives which cause a rapid loss of blood pressure may stimulate the production of epinephrine or of norepinephrine and such a result has caused cerebrovascular episodes and pulmonary edema. Removal of pheochromocytoma cures paroxysmal hypertension, except in those who have combined effects from pheochromocytoma and essential hypertension.

Dr. Roth also said: (1) that pheochromocytoma is rarely found in the obese; (2) that palpitation when lying on one side may be the result of pheochromocytoma on the opposite side; (3) that she preferred the transabdominal route for exploration to establish the presence or absence of more than one tumor; (4) a drop in blood pressure followed by a rapid rise after the removal of one pheochromocytoma indicates the likelihood of another elsewhere.

Dr. Moyer discussed nephrectomy for acute renal vascular obstructive disease. He pointed out that as a rule renal vascular obstruction is only one part of the clinical picture. Those with renal vascular obstruction usually have aortic vascular occlusive disease as the basis for the renal vascular disease. In his experience 80 to 90 per cent of those having this condition also have arteriosclerotic disease of the coronary or cerebral vessels. Many of these succumb to coronary disease. Even if operated for the vascular occlusion, the renal disease progresses in a large proportion of those who do not succumb to the coronary disease. The indications for study of suspected renal vascular occlusion is difficult to define. In general, his criteria for study are progressive increase in diastolic pressure in a younger person and rapid acceleration of hypertension in later life. Moreover, he pointed out that the study of differential sodium excretion is of value only in unilateral disease and that 20 per cent of those tested developed complicating pyelonephritis. He reported that vascular bypass is a preferred technique for repair because it does not interfere with renal flow and it adds to the circulatory renal volume. It is also a safeguard against the failure of the bypass. He briefly discussed diuretic therapy for hypertension of renal origin where he advised the use of hydrochlorothiazide with hydralazine (25 mg. b.i.d.) and where this therapy is ineffective guanethidine is to be added. In his experience the treatment for hypertension of renal origin is more effective than in essential hypertension.

Dr. Medelman concluded the discussion by pointing out that aortograms determine the need for treatment and that percutaneous femoral aortography was the technique of choice. He considered a relatively small change in the size of the kidney important in the diagnosis of unilateral renal vascular occlusive disease. He classified the renal occlusive disease as: (1) intrinsic, to include plaques and thromboses; (2) submuscular hyperplasia, and, (3) extrinsic to include aneurysm of the renal artery, tumor pressing on the renal artery, thrombosis of the aorta producing pressure on the renal artery.

Management of Inoperable Carcinoma of the Lung

Moderator: Richard H. Overholt, Boston
Panel: John Boland, New York City
John K. Fulton, Wichita
Robert B. Golbey, New York City
Phineas J. Sparer, Memphis

All panelists agreed with Dr. Overholt that something positive and constructive should be done in patients with inoperable carcinoma of the lung.

One answer to the problem is super-voltage radiation therapy. Less than 50 per cent of the patients survived after two years. In a few instances, a resection was possible after x-ray therapy. Preoperative radiation is very helpful in many instances, but in "coin" lesions of the lung this should be avoided.

Dr. Overholt mentioned that neither recurrent laryngeal nerve paralysis nor distant extrathoracic node involvement always mean inoperability. He has few five year survivals of patients who had both recurrent-laryngeal nerve paralysis and positive scalene node biopsy.

Chemotherapy is only palliative. The drug of choice is nitrogen mustard which frequently relieves pain and obstructive lesions.

The psychiatrist's approach to the problem of the dying patient is to give the truth as one would give medicine, little by little, not all at once; to deal with his fears and anxieties rather than concern oneself with his education.

It is not what one says to the patient that counts, but how one says it. From the patient's point of view, dying may not appear as tragic after all, and they expect the physicians to give strength and security, instead of creating inter-personal barriers by falsehoods and half truths.

Current Trends in Treatment or Prophylaxis of Rheumatic Fever

Moderator: Gene Stollerman, Chicago
Panel: Antoni M. Diehl, Kansas City
Raphael N. Paul, Memphis
Robert F. Ziegler, Detroit

In recent years, there has been a decreased incidence of rheumatic fever. Children with a less severe attack of streptococcus have less incidence of rheumatic fever. Post-streptococcal continuing disease is not rheumatic fever and must be distinguished. It was felt that the diagnosis of rheumatic fever must be questioned unless there is carditis.

The epidemiology of rheumatic fever is determined by (1) antibody titre and (2) the nature of the streptococcal strain. In one study, 40 per cent of the time it was thought that the exudative pharyngitis was streptococcal in origin and was due to a virus.

Rheumatic fever may be seen with streptococcal strains that cannot be typed. Confusion occurs if we use only throat cultures and not an antibody rise. Without a culture, the clinician is only 20 per cent correct.

The optimal blood level for killing the streptococcus is 0.04 units of penicillin, but it is the ***duration***, not the level above this figure, that is important. Erythromycin is the drug of choice if the patient is allergic to penicillin.

If the children do not get carditis with the first attack, they usually do not get it with the second.

Auscultation is the primary basis for diagnosing rheumatic carditis.

Thoracic Surgical Emergencies in Infants (Cine Symposium)

Roy F. Goddard, Albuquerque, was the moderator of this session. Members of the panel were: Johann L. Ehrenhaft, Iowa City; Paul H. Holinger, Chicago, Milton I. Levine, New York City, and Harvey White, Chicago. Dr. White pointed out the value of cine-fluorography as an important diagnostic tool in tracheo-esophageal fistula and esophageal atresia. Emphasis was placed on its importance in problems of regurgitation and dysphagia in the newborn and early infancy, not only in the above conditions, but also in congenital hiatal hernia. The significance of pneumothorax congenitally, cystic diseases of the lung with emphysema and congenital intrathoracic tumors were eloquently described. Respiratory obstruction in its supraglottic, glottic and infraglottic phases was methodically presented through beautiful color-bronchoesophagology-photography by Dr. Holinger. The pediatrician's role in collaboration with the surgeon in terms of diagnosis, treatment and joint effort was completely agreed upon. Cooperative efforts spell out accurate diagnosis, with a lessening in mortality and morbidity in the newborn and the young.

Symposium on Medical Aspects of Air Pollution

Moderator: Seymour M. Farber, San Francisco
Panel: Robert J. Anderson, Washington, D. C.
G. W. H. Schepers, Wilmington, Delaware
W. C. Hueper, Bethesda, Maryland

Dr. Farber emphasized the need for considering the broad implications of air as a major part of our environment. He stressed not only the enormous exposure of the lung to air and its contents, but the importance of air pollution in our whole ecology. These factors can only be understood and evaluated by a multi-disciplinary approach.

Dr. Anderson submitted the thesis that we are well on the way to establishing proof that air pollution can and does adversely affect human health. Caution in interpreting cause and effect led him to propose these criteria for studying effects of air pollution:

(1) Statistical evidence that a disease or condition exists in the population.
(2) Epidemiological evidence of the association between this disease or condition and a certain factor or factors present.
(3) Laboratory demonstration that this factor or factors can produce a condition in experimental subjects—similar to that found in the population.
(4) The ultimate demonstration that protection from this factor or factors will lessen the amount or severity of the disease conditions present.

Dr. Schepers discussed particulate matter in terms of size, retention and reaction in the lung, synergism, antagonism and biological variability. He gave special importance to three factors that must be considered in the relation of particulate matter and impairment of health:

(1) The progression of lung reactions after cessation of exposure.
(2) The breakdown of biological defenses that may occur.
(3) The fact that a particle breathed into the lung may be redeposited elsewhere.

Dr. Hueper discussed the evidence implicating various chemicals produced in industrial operations which are responsible for the occurrence of cancers of the respiratory tract among members of worker groups inhaling them with the plant atmosphere. He emphasized the concept of "a polyetiology of lung cancers which varies with the quantitative and qualitative aspects of the locally prevailing environmental respiratory carcinogenic spectrum."

Open Heart Surgery at Profound Levels of Hypothermia

Gumersindo Blanco-Dalmau, Philadelphia, discussed profound hypothermia and stated it provides a quiet, bloodless field for the surgeon operating within the heart. Cooling may be accomplished by use of a standard pump-oxygenator and heat exchanger or by a technic of autogenous oxygenation where the lung supplants the artificial oxygenator. He emphasized that during profound hypothermia, the circulation may be interrupted safely for periods up to one hour. Also, he pointed out the need for the differential cooling of various organs, with particular reference to brain temperature.

Micro-Niacin Test for Distinguishing Mycobacteria

Maurice S. Tarshis, Alexandria, Louisiana, reported on a comparative study of the usefulness of three recently reported micro-niacin tests using both freshly isolated and stored cultures of various types of mycobacteria. When performed on the fresh cultures, it was observed that all of the human type tubercle bacilli yielded slightly to intensely positive tests, whereas, all of the other strains, with two exceptions, gave either negative or doubtful results. As the period of incubation increased, there was a corresponding increase in both the number and degree of positive results. The bovine type tubercle bacilli exhibited slightly positive results with each test after the 10, 14 and 21-day periods respectively. The tests are simple, efficient, safe, and economical. Reproducible and consistent results can be obtained on cultures as old as three years. In most instances, the results exhibited by human tubercle bacilli are sufficiently different in character from the results produced by other mycobacteria to enable a clear-cut differentiation of these organisms.

Pulmonary Interstitial Emphysema in the Newborn

Paul A. Kirschner and Lotte Strauss, New York City, reported that in over 500 consecutive necropsies performed on live-born infants dying within seven days of birth, pulmonary interstitial emphysema and/or pneumothorax was encountered more than 40 times. Ten of these 40 babies had hypoplastic lungs, a congenital anomaly prone to develop emphysema, and incompatible with life. It is striking that over 30 babies had anatomically normal lungs. Pulmonary interstitial emphysema occurs quite commonly in relatively mature infants. Seventeen of 65 newborns weighing over 2500 gm. were affected. It becomes manifest clinically when one or both of its sequelae develop. These sequelae are pneumomediastinum and pneumothorax. During the seven-year period encompassing this series of necropsies, pneumothorax was diagnosed clinically in 11 babies. There were four recoveries and seven deaths in this group. The mechanism underlying the development of pulmonary interstitial emphysema appears to be a rise in intrabronchial and intra-alveolar pressure. This may be focal or diffuse. Such pressure rise may be caused by retained or aspirated secretions, inflammatory exudates, unequal aeration, forced irregular respiratory efforts and resuscitative measures alone or in combination.

Gas Exchange during Exercise in Patients with Diffuse Obstructive Pulmonary Emphysema

The standard Baldwin-Cournand exercise test was modified by John W. Vance, Buffalo, for use in the partial evaluation of patients. Collection of expired air was segmented into intervals of one minute or so, as indicated. This has allowed evaluation of the time-course of oxygen uptake, CO_2 output, and respiratory exchange ratio, during the transient unsteady state caused by the exercise and during the recovery period. Gas exchange was calculated according to the work performed. Definite patterns emerged which separated those patients with pulmonary emphysema from normal subjects. These patterns seemed to emerge fairly early in the course of disease, often before appreciable disability existed.

CHAPTER NEWS

Pacific Northwest Chapter

The Pacific Northwest Chapter will hold its annual meeting at the University of Oregon Medical School Library, Portland, October 27-28. The program follows:

Friday, October 27

8:00 a.m. Registration

9:00 a.m. Morning Session
Waldo Mills, Seattle, Chairman
Cigarette Smoking Among School Students
Albert R. Allen, Selah, Washington
Discussion: Joseph Matarazzo, Portland
Bronchogenic Carcinoma
A. Soltas and Elliott W. Harrison, Vancouver, B. C.
Discussion
Experiences in Treatment of Aortic Valve Lesions by the Open Heart Method
Ralph Berg, Jr., Spokane
Discussion
Selection of Patients for Open Heart Mitral Valve Surgery—Late Results following Mitral Replacement with the Starr-Edwards Prosthesis
Herbert E. Griswold, Albert Starr, J. David Bristow, Victor D. Menashe and Zaven A. Adrouny, Portland
Discussion
Open Heart Surgical Correction of Tetralogy of Fallot
Peter Allen, Vancouver, B. C.
Hemodynamic Studies after Total Correction of Tetralogy of Fallot
J. David Bristow, Zaven A. Adrouny, George A. Porter, Victor D. Menashe, Albert Starr and Herbert E. Griswold, Portland, Oregon
Discussion of tetralogy of Fallot papers to be opened by:
Albert Starr, Portland, Oregon

11:50 a.m. Business meeting

1:30 p.m. Afternoon Session
J. D. Galbraith, Sardis, B. C., Chairman
Farmer's Lung
C. J. Fuller, Exeter, England
Discussion
Thymic Tumors in the Adult
Glenn M. Gordon, Eugene, Oregon
Discussion
Management of Abnormalities of Pulmonary Venous Drainage
P. G. Ashmore, Vancouver, B. C.
Discussion
Factors Influencing Recovery following Pulmonary Resection
G. Hugh Lawrence, Seattle
Discussion
Parakeet Dander Pneumonitis
Edward H. Morgan, H. Rowland Pearsall, H. Tesluk and Dorothy Beggs, Seattle
Discussion
X-ray Conference
Moderator: Morton Goodman, Portland

Saturday, October 28

8:30 a.m. Morning Session
Kenneth A. Tyler, Gooding, Idaho, Chairman
Pericardial Effusion
Marvin Schwartz and William Hurst, Portland
Discussion
Surgical Anatomy of the Pulmonary Hilum, Part II (Motion Picture)
Franklin R. Smith, Seattle
Traumatic Aneurysms of the Aorta
Stanley F. Bergquist, Portland
Discussion
A Study of Intermittent Positive Pressure Breathing
James Morris, Portland
Discussion
Medical Aspects of the Air We Breathe
Seymour M. Farber, San Francisco
Discussion
Bacterial Contamination of Oxygen
JD Mortensen, Gloria Hurd and Gilbert Hall, Salt Lake City
Discussion: Arthur Frisch, Portland

Diagnosis of Congenital Heart Disease by Use of a Digital Computer in Solving Probability Equations
L. George Veasy, Homer Warner and Alan Toronto, Salt Lake City
Discussion
Critical Evaluation of Procaine Amide in Ventricular Fibrillation
Russell M. Nelson, Salt Lake City
Clinical Significance of the Size of the Tuberculin Test
J. D. Galbraith, Sardis, B. C.
Discussion of preceding two papers

Pennsylvania Chapter

The Pennsylvania Chapter of the College will meet in conjunction with the annual meeting of the Pennsylvania Medical Society in Pittsburgh, October 19, at the Penn-Sheraton Hotel. The chapter will sponsor the following program commencing at 1:00 p.m.:

Archibald C. Cohen, Butler, Chapter president, presiding
Hospital Infections
Howard H. Steele, Philadelphia
Steroids in the Treatment of Pulmonary Tuberculosis
A. A. Abbatiello, Butler
The Psychiatrist's Contribution to the Management of Patients with Pulmonary Tuberculosis
Victor J. Freeman, Pittsburgh
Practical Pulmonary Function Tests
E. D. Robin, Pittsburgh
Panel discussion: Tuberculosis as It Is Today
Moderator: Gilmore M. Sanes, Pittsburgh
Panel: W. Roderick Brown, Pittsburgh
Harold E. Coder, Harrisburg
Harold G. Curtis, Cleveland

A ten-minute discussion will follow each paper and there will be a business meeting at 5:00 p.m.

Potomac Chapter

The annual meeting of the Potomac Chapter will be held at the Sheraton-Baltimore Inn, Baltimore, on October 15. Dr. Edmund G. Beacham, Baltimore, program chairman, has announced that registration will open at 8 a.m. with the following scientific program:

9:00 a.m. Morning Session
Milton B. Kress, Baltimore, Chapter President, presiding
Chronic Bronchitis and Bronchiectasis (motion picture)
John E. Rayl, Oteen, North Carolina
Discussion: John H. Hirschfeld, Baltimore, and John E. Rayl
Prevalence of Histoplasmosis in Eastern United States
Charles Emmons and Herbert F. Hasenclever, Bethesda
Skin Testing Program and Follow-ups of Children in Eastern Maryland Area
John E. Baybutt, Easton
Discussion: John E. Baybutt and Charles Emmons
Recent Advances in Pulmonary Emphysema
Vernon Krahl, Baltimore
Discussion

12:00 noon Luncheon

1:00 p.m. Afternoon Session
John Trenis, Washington, D. C., Chapter Vice-President, presiding
Airway Foreign Body Management
Gabriel F. Tucker, Jr., Baltimore
Discussion
Chest Surgery in the Aged
Robert J. Wilder, Baltimore
Discussion: Otto C. Brantigan, Baltimore
Techniques of Left Heart Investigation
Leonard Scherlis, Baltimore
Cineangiography in Acquired Heart Disease
Richard Ross and Michael Criley, Baltimore
Discussion

3:30 p.m. Business meeting

Virginia Chapter

The Virginia Chapter will meet with the Medical Society of Virginia at the Hotel John Marshall, Richmond, October 9. The chapter will sponsor the lecture, "Steroid Treatment of Pulmonary Diseases," to be presented by Dr. Sol Katz of Washington, D. C., at 9:30 a.m.

Colorado Chapter

The program for the annual meeting of the Colorado Chapter of the College, to be held at the Bushnell Auditorium at Fitzsimons General Hospital, Denver, September 30, will be co-sponsored by the chapter, the Colorado Trudeau Society and Fitzsimons General Hospital, following the Pulmonary Disease Seminar at Fitzsimons General Hospital, September 25-29. The chapter program will consist of two panel discussions, the first on "Management of the Tuberculous Patient" to be moderated by William Russell, Denver, at 9 a.m.; the second is concerned with "Medical and Surgical Problems in the Management of the Aging Patient with Cardiopulmonary Disease" at 10:30, to be moderated by Colonel James A. Wier, Denver. Dr. Norman J. Wilson, Boston, will be a guest panelist on both panels. The chapter luncheon and business meeting will commence at 12:30 p.m.

Indiana Chapter

The annual meeting of the Indiana Chapter will be held at the Columbia Club, Indianapolis, on Tuesday, October 24. Dr. John V. Thompson, Governor of the College for Indiana, has arranged the following program.

5:30 p.m. Cocktail Party and Dinner

7:00 p.m. Panel Discussion

Management of the Cardiopulmonary Cripple

Moderator: Andrew L. Banyai, Chicago

Panel: John F. Briggs, St. Paul
Edwin P. Levine, Chicago
Herman J. Moersch, Rochester, Minnesota
Leon Unger, Chicago

Questions from the floor

8:00 p.m. Fireside Conferences

Upon invitation by the Indiana State Medical Association, the Chapter and the state society will join for the first time in presenting these popular "Fireside Conferences." The following subjects will be discussed:

Emphysema and Unusual Pulmonary Diseases
Pulmonary Tuberculosis and Fungus Disease
Industrial Diseases of the Lung
Trauma of the Thorax
Intrathoracic Tumors
Major Arterial Disease
Congenital Heart Disease
Rheumatic Heart Disease
Coronary Disease
Cardiac Arrhythmias and Decompensation

Refreshments will be served with the compliments of the Indiana Chapter.

Michigan Chapter

Members of the Michigan Chapter will meet at the Pantland Hotel, Grand Rapids, September 27 for dinner. Dr. Arthur J. Vorwald, Detroit, will moderate a discussion on "Difficult Diagnosis as Related to Chest Disease."

CALENDAR OF EVENTS

National and International Meetings

Interim Session, American College of Chest Physicians
Denver, Colorado, November 25-26, 1961

7th International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
New Delhi, India, February 20-24, 1963

Postgraduate Courses

Occupational Diseases of the Chest
Philadelphia, September 25-29

Clinical Cardiopulmonary Physiology
Chicago, October 23-27

Recent Advances in the Diagnosis and Treatment of Heart and Lung Diseases
New York City, November 13-17

Recent Advances in the Diagnosis and Treatment of Heart and Lung Diseases
Los Angeles, December 4-8

Chapter Meetings

Illinois Chapter, Chicago, September 27
Michigan Chapter, Grand Rapids, September 27
Colorado Chapter, Denver, September 30
Virginia Chapter, Richmond, October 9
New England States Chapter, Portland, Maine, October 15
Potomac Chapter, Baltimore, October 15
Pennsylvania Chapter, Pittsburgh, October 19
Indiana Chapter, Indianapolis, October 24
Pacific Northwest Chapter, Portland, Oregon, October 27-28
Southern Chapter, Dallas, November 4-5

COLLEGE INTERIM SESSION

The 1961 interim session of the College will be held at the Brown Palace Hotel, Denver, on Saturday and Sunday, November 25 and 26. The American Medical Association will hold its clinical session in Denver, November 27 through 30. Physicians who plan to attend the College meeting may write directly to the Brown Palace Hotel for reservations, indicating exact arrival and departure dates.

The following scientific program has been prepared under the direction of Dr. Hollis E. Johnson, Nashville, President of the College, including formal papers, panel discussions, round table luncheons and the popular fireside conferences. A dinner sponsored by the Colorado Chapter of the College will be held on Saturday night, and the fireside conferences will take place on Sunday night. Members are urged to make reservations in advance for the round table luncheons of their choice, as well as for the dinner, to which the ladies are invited.

A joint luncheon meeting of the Board of Regents and Board of Governors of the College will be held at noon on Saturday, November 25, and the semi-annual meeting of the Board of Regents will follow at 2:00 p.m. Members of the Board of Governors are cordially invited to attend the Regents' meeting where reports of the council and committee meetings held at the New York City session will be reviewed and acted upon.

Attention is called to the ADVANCE REGISTRATION AND RESERVATION FORM appearing on page 358 of this issue of the journal. Please complete this form at once and return it to the Executive Offices of the College in Chicago. Your badge, program and tickets will be awaiting your arrival at the College Registration Desk in the Brown Palace Hotel.

Program

SATURDAY, NOVEMBER 25

8:30 a.m. — REGISTRATION

8:55 a.m. — SCIENTIFIC SESSION

Co-Chairmen: **Carl W. Tempel,** Maj. Gen., MC, USA, Denver
Roger S. Mitchell, Denver

9:00 a.m. — PANEL DISCUSSION

Coronary Insufficiency: Diagnosis and Treatment

Moderator: **George R. Herrmann,** Professor of Medicine and Director, Cardiovascular Research Laboratory, University of Texas, Galveston

Panel: **Crawford W. Adams,** Assistant Clinical Professor of Medicine, Vanderbilt University, Nashville
John H. Moyer, Professor and Chairman, Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia
Ralph E. Smith, Assistant Professor of Medicine, Mayo Foundation, University of Minnesota, Rochester

QUESTIONS FROM THE FLOOR

9:45 a.m. — ***Abnormalities of the Pulmonary Artery Resembling Intrathoracic Tumors***

William B. Buckingham, Instructor in Medicine, Northwestern University, Chicago

10:05 a.m. — ***Chelating Drugs in Clinical Cardiology***

Alfred Soffer, Chief, Cardiopulmonary Laboratory, The Rochester General Hospital, Rochester, New York

10:25 a.m. — ***Ventilatory Effect of Headward Tilt of Thorax and Increased Intra-abdominal Pressure Breathing Air and 100 Per Cent Oxygen in Emphysema***

Gustav J. Beck, Instructor in Medicine and Alvan L. Barach, Clinical Professor of Medicine, Emeritus, Columbia University, New York

10:45 a.m. — ***Adequate Treatment of Spontaneous Pneumothorax***

Karl P. Klassen, Professor and Chief, Division of Thoracic Surgery, Ohio State University, Columbus

THERE WILL BE A FIVE-MINUTE DISCUSSION FOLLOWING EACH PRESENTATION

11:05 a.m. — PANEL DISCUSSION

Bronchitis, Bronchospasm and Bronchial Asthma

Moedrator: **Harry L. Rogers,** Assistant Professor of Clinical Medicine (Honorary), Jefferson Medical College, Philadelphia

Panel: **Edwin R. Levine,** Assistant Professor of Clinical Medicine, The Chicago Medical School, Chicago
B. T. McMahon, Assistant Clinical Professor of Medicine, University of Colorado, Denver
Edward H. Morgan, The Mason Clinic, Seattle
Theodore H. Noehren, Assistant Professor of Medicine, University of Buffalo, Buffalo

QUESTIONS FROM THE FLOOR

ADMINISTRATIVE MEETINGS—SATURDAY, NOVEMBER 25

8:00 a.m. — BREAKFAST MEETING—Committee on College Medal
J. Arthur Myers, Minneapolis, Chairman

12:00 noon— LUNCHEON—Board of Regents and Board of Governors
Howell S. Randolph, Phoenix, Chairman, Board of Governors, presiding

2:00 p.m. — Semi-Annual Meeting, Board of Regents
Arthur M. Olsen, Rochester, Minnesota, Chairman, presiding
Members of the Board of Governors are invited to attend the meeting of the Board of Regents.

5:00 p.m. — Meeting, Committee on Nominations
Edward H. Morgan, Seattle, Chairman

SATURDAY EVENING

7:30 p.m. — DINNER
SPONSORED BY THE COLORADO CHAPTER OF THE COLLEGE
This is strictly a social function—no speeches—the ladies are invited. There will be dancing after dinner.

SUNDAY, NOVEMBER 26

12:00 noon— ROUND TABLE LUNCHEON DISCUSSIONS

1) **DISEASES OF THE ESOPHAGUS**
Moderator: **Alfred Goldman**, Attending Thoracic Surgeon, Cedars of Lebanon Hospital, Los Angeles
Panel: **William E. Adams**, Professor and Head, Department of Surgery, University of Chicago, Chicago
Herman J. Moersch, Professor Emeritus, Mayo Foundation, University of Minnesota, Rochester
Norman J. Wilson, Overholt Thoracic Clinic, Boston
Roy G. Klepser, Associate Professor of Thoracic Surgery, Georgetown University, Washington, D. C.

2) **PAROXYSMAL TACHYCARDIA**
Moderator: **Friedrich W. Niehaus**, Professor of Internal Medicine, University of Nebraska, Omaha
Panel: **Eliot Corday**, Assistant Clinical Professor of Medicine, University of California, Los Angeles
Rudolph E. Fremont, Chief, Cardiovascular Section, Veterans Administration Hospital, Brooklyn
Aldo A. Luisada, Professor of Medicine, The Chicago Medical School, Chicago

3) **CHRONIC COR PULMONALE**
Moderator: **Burgess L. Gordon**, Visiting Physician, Jefferson Medical College (Philadelphia), Chicago
Panel: **David Goldfinger**, Assistant Professor of Medicine, The Chicago Medical School, Chicago
Arthur M. Olsen, Professor of Medicine, Mayo Foundation, Graduate School of Medicine, University of Minnesota, Rochester
Samuel A. Weisman, Clinical Associate Professor of Medicine, University of Southern California, Los Angeles

4) **CARCINOMA OF THE LUNG**
Moderator: **Hollis E. Johnson**, Professor Emeritus of Clinical Medicine, Vanderbilt University, Nashville
Panel: **Lawrence M. Lowell**, Associate Clinical Professor of Surgery, University of Oregon, Portland
Arnold B. Rilance, Assistant Clinical Professor of Medicine, Yale University, New Haven, Connecticut
John V. Thompson, Consultant, Thoracic Surgery, Community Hospital, Indianapolis

NOTE: Seating capacity at the round table luncheons is limited and reservations will be accepted in the order received. Please complete coupon on page 358.

1:55 p.m. — SCIENTIFIC SESSION
Co-Chairmen: **Leroy Elrick**, Denver
W. Bernard Yegge, Denver

2:00 p.m. — PANEL DISCUSSION
Evaluation of Drugs for the Treatment of Heart Failure
Moderator: **John F. Briggs**, Associate Professor of Clinical Medicine, University of Minnesota (Minneapolis), St. Paul
Panel: **James H. Hammond**, Col., MC, USAF, U. S. Air Force Hospital, MacDill Air Force Base, Tampa
James F. Moorman, Associate Professor of Medicine, University of Oklahoma, Oklahoma City
Merritt B. Whitten, Assistant Professor of Medicine, University of Texas, Dallas
QUESTIONS FROM THE FLOOR

2:45 p.m. — ***Medical Aspects of Air Pollution***

Seymour M. Farber, Chief, Tuberculosis and Chest Service, University of California, San Francisco General Hospital, San Francisco

3:05 p.m. — ***Pathogenicity Studies of Group III ("Battey") Mycobacteria from Pulmonary Lesions of Man***

William Feldman, Chief, Laboratory Research in Pulmonary Diseases, Department of Medicine and Surgery, Veterans Administration, and Roy E. Ritts, Department of Microbiology, Georgetown University, Washington, D. C.

3:25 p.m. — ***Pointers on X-ray Diagnosis of Lung Diseases***

Coleman B. Rabin, Consultant Physician for Chest Diseases, The Mount Sinai Hospital, New York City

3:45 p.m. — ***Prognosis in Children Who Reacted to Tuberculin at the Age of Five Years or Younger***

J. Arthur Myers, Professor Emeritus, Department of Medicine, School of Public Health, University of Minnesota

THERE WILL BE A FIVE-MINUTE DISCUSSION FOLLOWING EACH PRESENTATION

4:05 p.m. — **PANEL DISCUSSION**

Inhalation Therapy

Moderator: **Albert H. Andrews,** Clinical Associate Professor of Bronchoesophagology, Department of Otolaryngology, University of Illinois, Chicago

Panel: **Robert L. Grissom,** Professor and Chairman, Department of Internal Medicine, University of Nebraska, Omaha
Peter A. Theodos, Assistant Professor of Clinical Medicine, Jefferson Medical College, Philadelphia
William A. Zavod, Associate Clinical Professor of Medicine, Albert Einstein College of Medicine (New York City), Mount Vernon, New York

QUESTIONS FROM THE FLOOR

8:00 p.m. — **FIRESIDE CONFERENCES**

SUBJECTS AND DISCUSSION LEADERS

1) **OCCUPATIONAL FITNESS AFTER CORONARY DISEASE**

Moderator: **Grace M. Roth,** Lovelace Clinic, Albuquerque
Milton W. Anderson, Consultant in Medicine, Mayo Clinic, Rochester, Minnesota
Michael Bernreiter, Assistant Clinical Professor of Medicine, University of Kansas, Kansas City
Arthur Bernstein, Director and Attending Physician, Heart Institute, United Hospitals, Newark
Henry A. Bradford, Assistant Clinical Professor of Medicine, University of Colorado, Denver
James R. Fox, Instructor and Clinical Physician, Director of Medical Programming, University of Minnesota, Minneapolis

2) **TREATMENT OF HYPERTENSION**

Moderator: **Oliver K. Niess,** Major General, MC, USAF, The Surgeon General, United States Air Force, Washington, D. C.
Graham Asher, Cardiologist, Baptist Memorial Hospital, Kansas City, Missouri
James A. Orbison, Col., MC, USA, Chief, Cardiology Service, Fitzsimons General Hospital, Denver
Rudolph T. Wagner, Senior Physician, Mt. Sinai Hospital, Miami
Irving Willner, Director of Chest Diseases, Emeritus, Board of Health, Newark

3) **RHEUMATIC HEART DISEASE**

Moderator: **Milton S. Saslaw,** Director of Medical Research, National Children's Cardiac Hospital, Miami
Roy H. Behnke, Associate Professor of Medicine, Indiana University, Indianapolis
Matthew L. Gibson, Assistant Professor of Pediatrics, University of Colorado (Denver), Aurora, Colorado
Robert E. Lane, Attending Physician, Pierce County Hospital, Tacoma, Washington
Eugene T. McEnery, Clinical Professor of Pediatrics, Loyola University, Chicago
Byron E. Pollock, Director, Medical Service, Denver General Hospital, Denver

4) CONGENITAL HEART DISEASE

Moderator: **Daniel F. Downing,** Associate Professor of Pediatrics, Hahnemann Medical College, Philadelphia

Antoni M. Diehl, Associate Professor of Pediatrics, University of Kansas, Kansas City
Johann L. Ehrenhaft, Professor of Surgery and Chairman, Division of Thoracic Surgery, University of Iowa, Iowa City
Murray S. Hoffman, Chief of Cardiology, National Jewish Hospital, Denver
Frederick M. Lindauer, Clinical Instructor in Medicine, Loyola University, Chicago
Elmer C. Rigby, Thoracic Surgeon, Queen of Angels Hospital, Los Angeles

5) EMPHYSEMA OF THE LUNG

Moderator: **Andrew L. Banyai,** Clinical Professor of Medicine Emeritus, Marquette University (Milwaukee), Chicago

Otto C. Brantigan, Chief Surgeon, Church Home and Hospital, Baltimore
H. Dumont Clark, Associate Clinical Professor of Medicine, University of Colorado, Denver
Thomas S. Fleming, Chief of Medical Service, Woodland Hospital and Clinic, Moberly, Missouri
Donald R. McKay, Associate Clinical Professor of Medicine, University of Buffalo, Buffalo
Roger S. Mitchell, Associate Professor of Medicine, University of Colorado, Denver
William R. Rumel, Associate Clinical Professor of Surgery (Thoracic), and Chairman, Division of Thoracic Surgery, University of Utah, Salt Lake City

6) FUNGUS DISEASES OF THE LUNG

Moderator: **Michael L. Furcolow,** Chief, Kansas City Field Station, U. S. Public Health Service, Kansas City, Kansas

Elmore M. Aronstam, Lt. Col., MC, USA, Chief, Thoracic and Cardiovascular Surgery, Fitzsimons General Hospital, Denver
Oren A. Beatty, Hospital Director, District Two State Tuberculosis Hospital, Louisville
Alvis E. Greer, Professor Emeritus of Clinical Medicine, Baylor University, Houston
R. Drew Miller, Assistant Director, Mayo Foundation, University of Minnesota Graduate School, Rochester
Henry C. Sweany, Director of Research, Missouri State Sanatorium, Mount Vernon

7) PLEURAL EFFUSION: DIFFERENTIAL DIAGNOSIS

Moderator: **David B. Radner,** Director, Chest Department, Michael Reese Hospital and Medical Center, Chicago

Laszlo S. Arany, Director, Professional Services, Veterans Administration Hospital, Excelsior Springs, Missouri
Orin J. Farness, Internist, Tucson Medical Center, Tucson
David Ulmar, Associate Professor of Clinical Medicine, New York University Postgraduate Medical School, New York City
James A. Weir, Col., MC, USA, Chief, Department of Medicine, Fitzsimons General Hospital, Denver

8) MODERN TREATMENT OF TUBERCULOSIS

Moderator: **Charles K. Petter,** Superintendent and Medical Director, Lake County Tuberculosis Sanatorium, Waukegan, Illinois

Otto L. Bettag, Medical Director, Du Page County Tuberculosis Sanatorium Board, Glen Ellyn, Illinois
William B. Condon, Associate Clinical Professor of Surgery, University of Colorado, Denver
Charles S. Christianson, Col., MC, USA, Chief, Pulmonary Disease Service, Fitzsimons General Hospital, Denver
Sumner S. Cohen, Clinical Assistant Professor of Medicine, University of Minnesota, Minneapolis

Note: The Fireside Conferences are informal and offer an opportunity for free discussion. Discussion leaders will be seated at tables with proper identification. Physicians may participate in the discussion of their choice, or move on to other discussions when and if they desire.

Interim Session

AMERICAN COLLEGE OF CHEST PHYSICIANS

Advance Registration and Reservation Form

AMERICAN COLLEGE OF CHEST PHYSICIANS
112 East Chestnut Street
Chicago 11, Illinois

My check in the amount of $_____ is enclosed for reservations at the following functions to be held at the Brown Palace Hotel, Denver, on Saturday and Sunday, November 25 and 26.

DINNER, Saturday, November 25 — **Tickets $5.50 each** (including tax and gratuity)

I wish to reserve_____places at the dinner.

ROUND TABLE LUNCHEONS, Sunday, November 26 — **Tickets $3.50 each** (including tax and gratuity)

First Choice _____ Second Choice _____

Please indicate choice by number as listed in the program

Applications for reservations at the Round Table Luncheons will be accepted in the order received. Tickets will be held at the College Registration Desk in the Brown Palace Hotel for pick-up.

Please make checks payable to the AMERICAN COLLEGE OF CHEST PHYSICIANS

THERE IS NO REGISTRATION FEE
ALL PHYSICIANS ARE CORDIALLY INVITED TO ATTEND

Member_____ Non-member_____

Name_____

Address_____

City/State_____

Accompanied by_____

Hotel_____

Arrival date_____ Departure date_____

Please return this form promptly, thank you.

For Hotel Reservations Please Write Directly to The Brown Palace Hotel